Candidoses invasives

Focus sur la réanimation

Michel Wolff

Hôpital St Anne, Paris, Mars 2022

Liens d’intérêt

Orateur pour des réunions organisées par des laboratoires pharmaceutiques

- ❑ GILEAD
- ❑ MSD
- ❑ ADVANZ

De quoi parle-t-on ?

- Candidémie: ≥ 1 hémoculture positive
- *Candida* dans un site sterile:

  - Péritoine
  - Os
  - Articulation
  - Œil
  - LCR…..

Candidoses invasives: les questions

1. Est-ce fréquent et quels sont les facteurs de risque?
2. Est-ce grave ?
3. Comment les diagnostiquer ?
4. Quand traiter?
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Candidoses invasives: les questions

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Bassetti *et al. Critical Care* (2019) 23:219
https://doi.org/10.1186/s13054-019-2497-3

Critical Care

RESEARCH Open Access

Incidence and outcome of invasive candidiasis in intensive care units (ICUs) in Europe: results of the EUCANDICU project

Results

Primary analysis—cumulative incidence

During the study period, the 23 ICUs (median number of beds 18, interquartile range 14–43) had 80,645 admissions and 570 episodes of ICU-acquired IC, corresponding to an incidence of 7.07 episodes per 1000 ICU admissions

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Volume 97, Issue 2, June 2020, 115016

Antimicrobial Susceptibility Studies

Bacterial and fungal pathogens isolated from patients with bloodstream infection: frequency of occurrence and antimicrobial susceptibility patterns from the SENTRY Antimicrobial Surveillance Program (2012–2017)

Michael A. Pfaller [a,b], Cecilia G. Carvalhaes [a,*], Caitlin J. Smith [a], Daniel J. Diekema [b], Mariana Castanheira [a]

Rank	Organism	Total (%)
1	*S. aureus*	1567 (22.5)
2	*Escherichia coli*	1473 (21.2)
3	*Enterococcus* spp.	695 (10)
4	*Klebsiella* spp.	636 (9.1)
5	CoNS	604 (8.7)
6	BHS	309 (4.4)
7	*P. aeruginosa*	293 (4.2)
8	*Enterobacter* spp.	261 (3.7)
9	*Candida* spp.	216 (3.1)
10	VGS	173 (2.5)
	Total	**6963**

Bassetti et al. Critical Care (2019) 23:219
https://doi.org/10.1186/s13054-019-2497-3

Critical Care

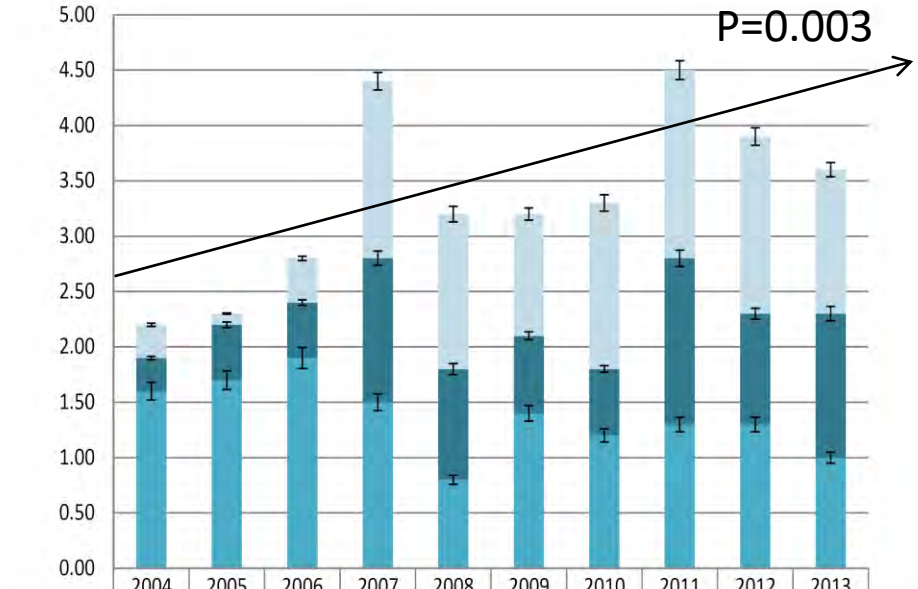
RESEARCH Open Access

Incidence and outcome of invasive candidiasis in intensive care units (ICUs) in Europe: results of the EUCANDICU project

Facteurs	
Chirurgie abdominales dans les 30 j	174 (53%)
Antibiotiques dans les 30 j	226 (68%)
Score SOFA	9 (IQR: 5–12)
AKI	157 (48)
DS en réanimation avant	8 (IQR: 3–19)

Incidence and risk factors of candidemia in ICU in France (National network: 213 ICU's)

/1000 pat.



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Other	0.30	0.10	0.40	1.60	1.40	1.10	1.50	1.70	1.60	1.30
Catheter	0.30	0.50	0.50	1.30	1.00	0.70	0.60	1.50	1.00	1.30
Unknown	1.60	1.70	1.90	1.50	0.80	1.40	1.20	1.30	1.30	1.00

Table 2 Risk factors of ICU-cand – Multivariable logistic regression stratified by center.

Parameter	OR (CI 95%)	p
Length of ICU stay		<0.0001
< 5 days		
5–7 days	3.3 (1.50–7.30)	
8–13 days	11.8 (5.7–24.4)	
2 weeks or more	66.8 (33.1–134.7)	
Years		0.0015
2004		
2005	0.99 (0.61–1.60)	
2006	1.34 (0.86–2.08)	
2007	2.05 (1.35–3.11)	
2008	1.41 (0.92–2.17)	
2009	1.34 (0.87–2.06)	
2010	1.19 (0.77–1.83)	
2011	1.72 (1.14–2.61)	
2012	1.52 (1.01–2.31)	
2013	1.39 (0.92–2.09)	
SAPS II score		<0.0001
0–28		
29–40	1.65 (1.17–2.32)	
41–53	2.04 (1.47–2.83)	
54–163	2.4 (1.74–3.31)	
Immune suppression		<0.0001
no		
neutropenia	2.61 (1.87–3.65)	
Other than neutropenia	1.79 (1.5–2.12)	
Patient origin		0.031
Home		
Long term facilities	0.78 (0.54–1.13)	
Ward	1.18 (1.02–1.37)	
Another ICU	1.25 (0.94–1.66)	
Antimicrobials at admission	1.76 (1.46–2.12)	<0.0001
Central venous catheter	2.01 (1.63–2.49)	<0.0001

Odds ratio: OR>1: increased risk of ICU-cand.

Baldesi O et al. *J Infect.* 2017 Mar 31. pii: S0163-4453(17)30103-2.

Facteurs de risque: réanimation/hors réanimation

Risk factors	Intensive care[1, 2] (N = 250)			Non-Intensive care[1, 2] (N = 322)		
	OR	95% CI	p	OR	95% CI	p
Central venous catheter[4]				9.77	3.72–25.7	< 0.001
Total parenteral nutrition[4]	6.75	2.89–15.7	< 0.001	3.29	1.52–7.13	0.003
Previous septic shock	2.39	1.14–5.01	0.02			
Acute kidney injury	4.77	1.94–11.8	< 0.001			
Heart disease	3.78	1.09–13.1	0.006			
Renal replacement therapy						
Glycopeptides[5, 6]				3.31	1.33–8.23	0.01
Nitroimidazoles[5, 6]				3.12	1.07–9.11	0.04
Aminoglycosides[5, 6]	2.28	1.01–5.13	0.05			

Poissy *et al. Critical Care* (2020) 24:109

Délai de survenue des candidoses invasives en réanimation

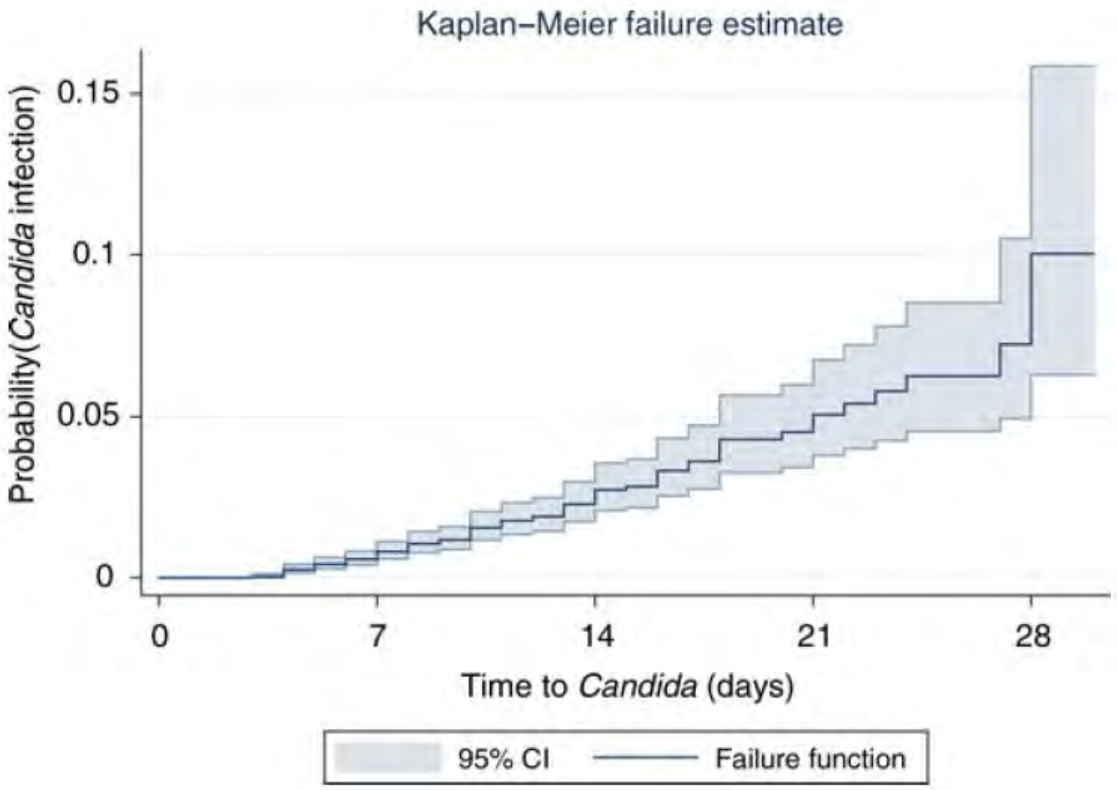
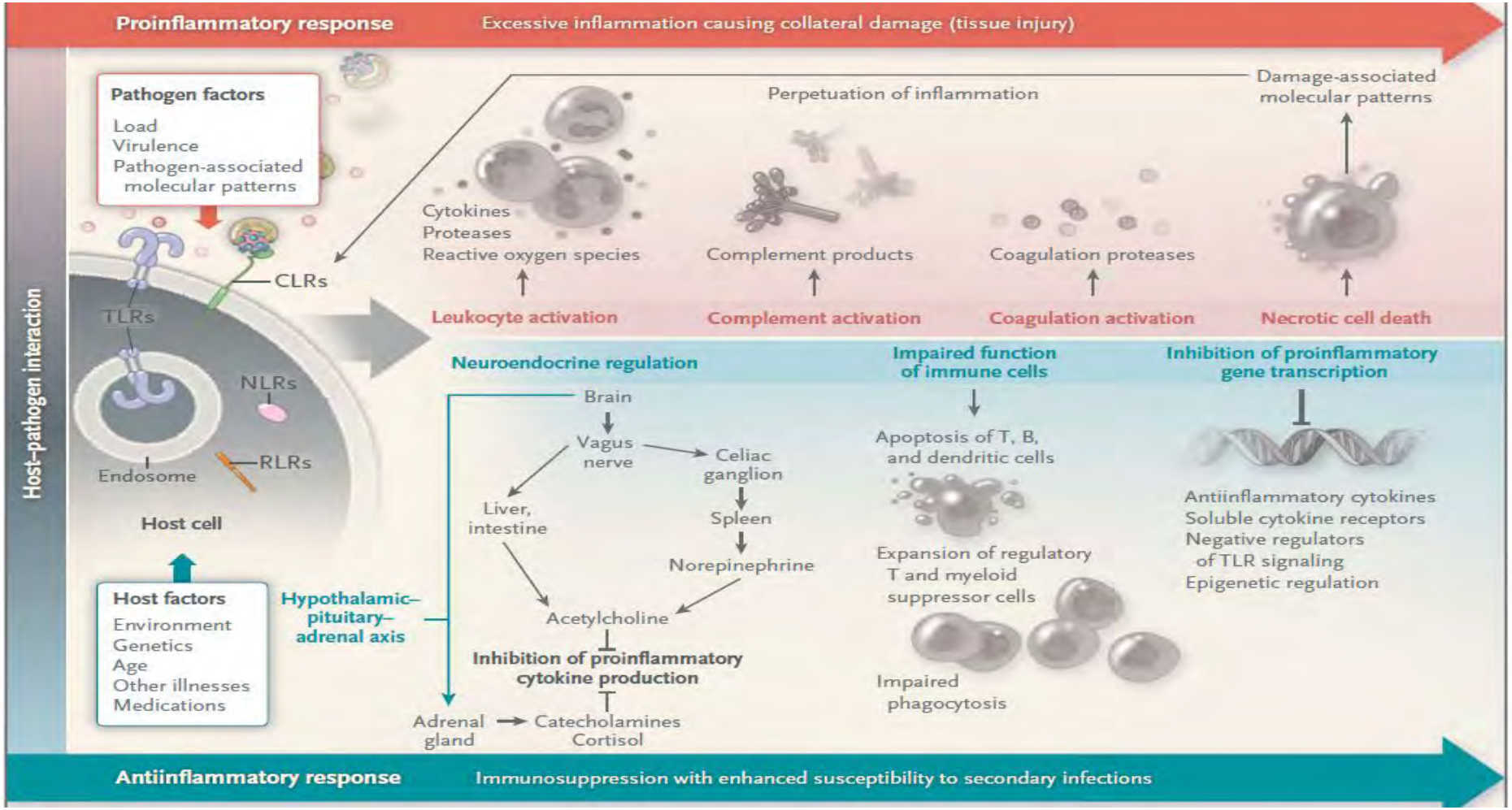


Figure 1. Time to development of invasive candidiasis across the 6685 patients in the cohort plotted against probability. After an initial delay, there is a relatively linear rise with time up to 28 days. Abbreviation: CI, confidence interval.

E. Geoffrey Playford, *Clinical Infectious Diseases* 2016



DC Angus et al. NEJM 2013

Fungal infections in mechanically ventilated patients with COVID-19 during the first wave: the French multicentre MYCOVID study

JP Gangneux et coll.

Lancet Respir Med 2022; 10: 180–90

Prevalence of infections	
CAPA*: pr/pb invasive aspergillosis	76 (15%)
pr/pb invasive fungal infection other than pr/pb CAPA (one or more)	38 (7%)
Candidemia	32 (6%)
Invasive mucormycosis	6 (1%)
Invasive fusariosis	1 (<1%)
Bacterial ventilator-associated pneumonia (n=509)†	374 (73%)
Cytomegalovirus infection (n=491)†	49 (10%)
Herpes simplex virus type 1 infection (n=491)†	76 (15%)

Intensive Care Med (2020) 46:2001–2014
https://doi.org/10.1007/s00134-020-06240-x

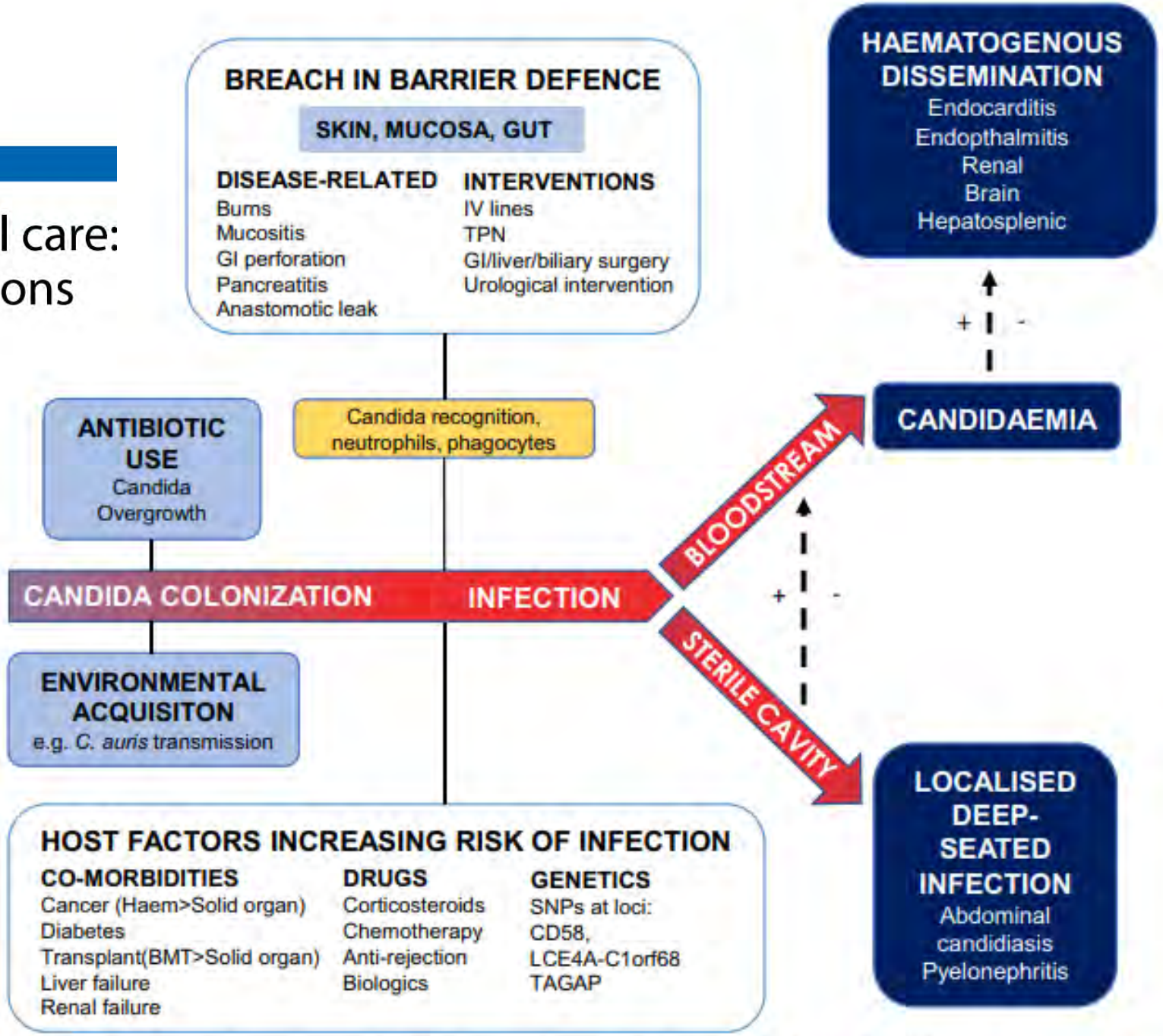
NARRATIVE REVIEW

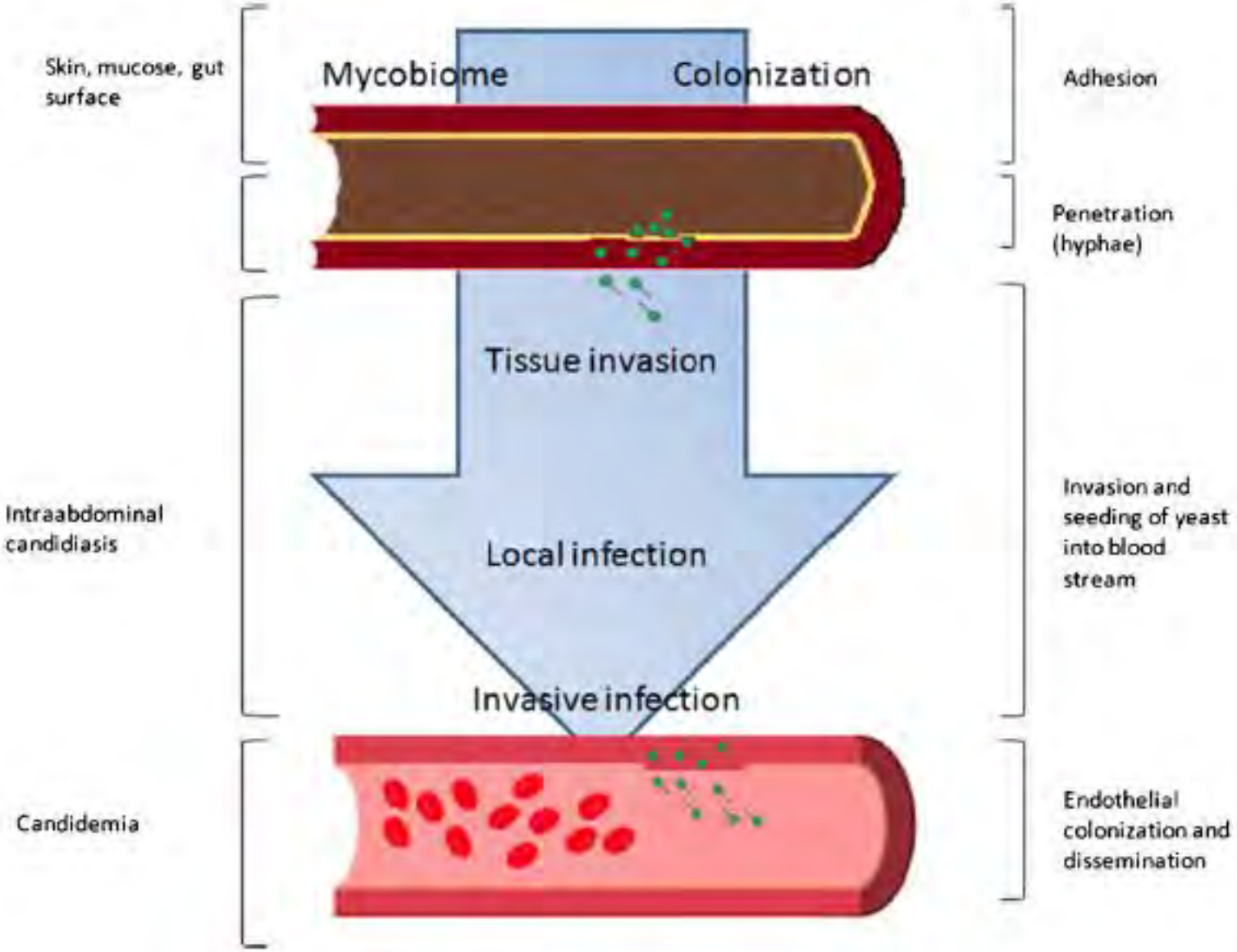
Invasive candidiasis in critical care: challenges and future directions

C. Logan[1,2], I. Martin-Loeches[3,4*] and T. Bicanic[1,2]

Endogènes
- Microbiote digestif: *C. albicans* *C. glabrata*
- Microbiote cutané: *C. parapsilosis*

Exogènes
C. tropicalis, C. kusei, C. keyfir, C. auris, C. lusitaniae

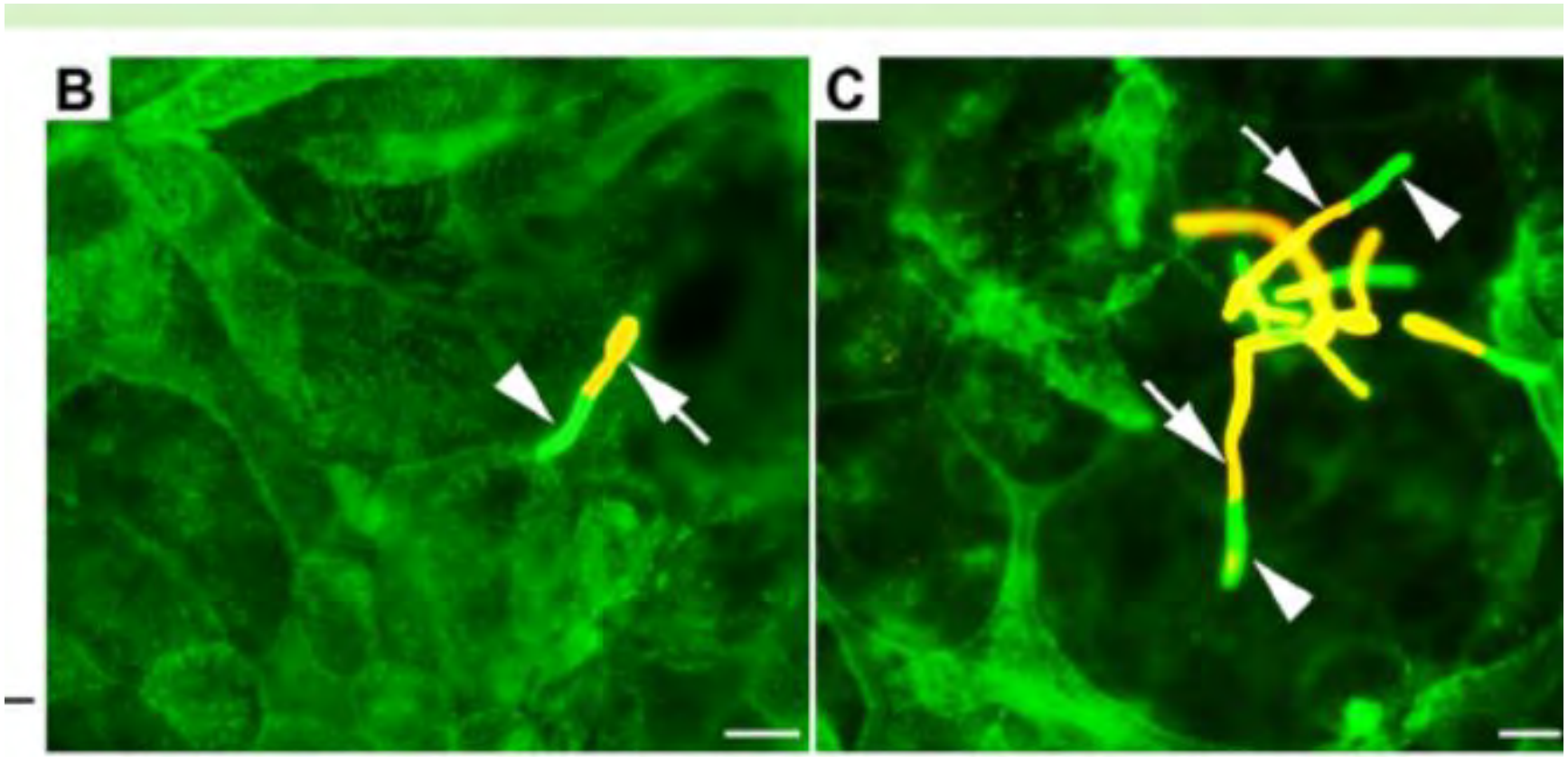




L Lagunes & J Rello, Eur J Clin Microb Infect Dis 2016

Cellular Microbiology (2016) **18**(2), 195–210
doi:10.1111/cmi.12495
First published online 31 August 2015

Candida albicans is able to use M cells as a portal of entry across the intestinal barrier *in vitro*



Message 1: les candidémies en réanimation sont des événements relativement peu fréquents, survenant après plusieurs jours de réanimation chez les patients les plus graves, souvent opérés et ayant reçu des antibiotiques

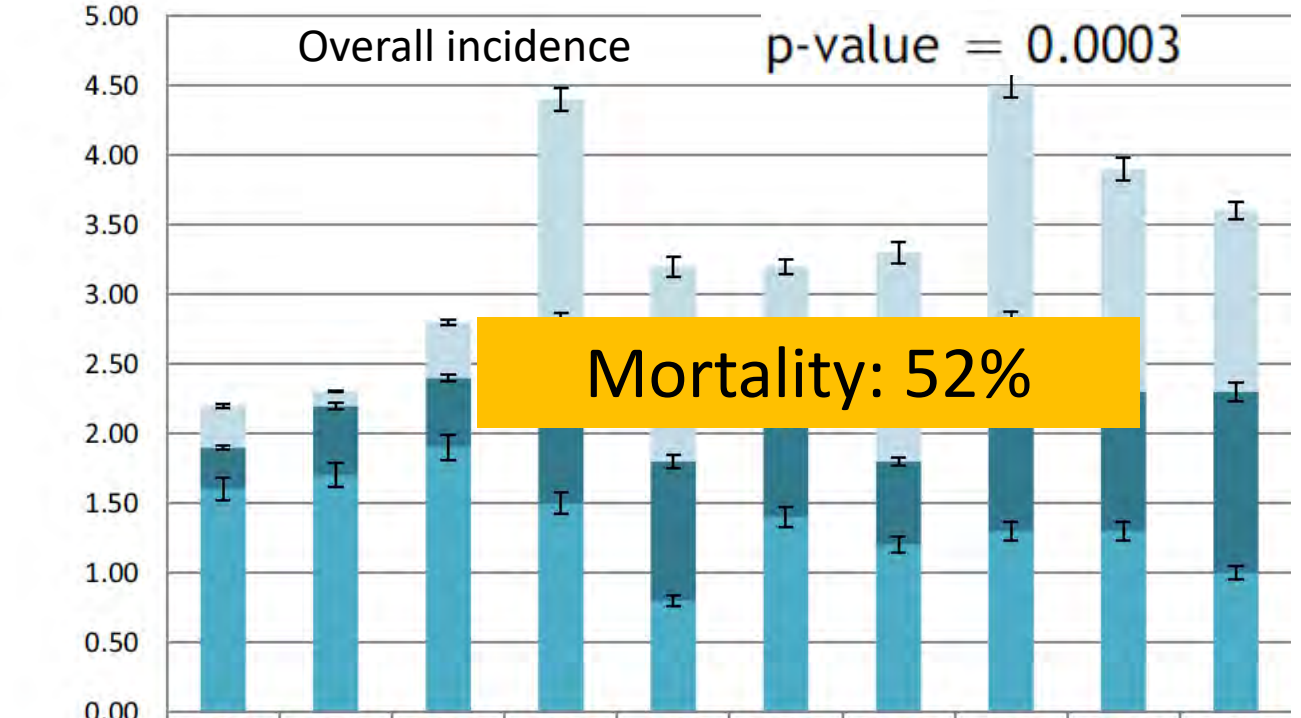
Candidémies: les questions

1. Est-ce fréquent et quels sont les facteurs de risque ??
2. Est-ce grave ?
3. Comment les diagnostiquer ?
4. Quand traiter?
5. Comment traiter ?

Journal of Infection (2017) 75, 59–67

ICU-acquired candidaemia in France: Epidemiology and temporal trends, 2004–2013 – A study from the REA-RAISIN network

Incidence of ICU candidaemia (per 1000 ICU admissions) from 2004 to 2013.



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
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Unknown	1.60	1.70	1.90	1.50	0.80	1.40	1.20	1.30	1.30	1.00

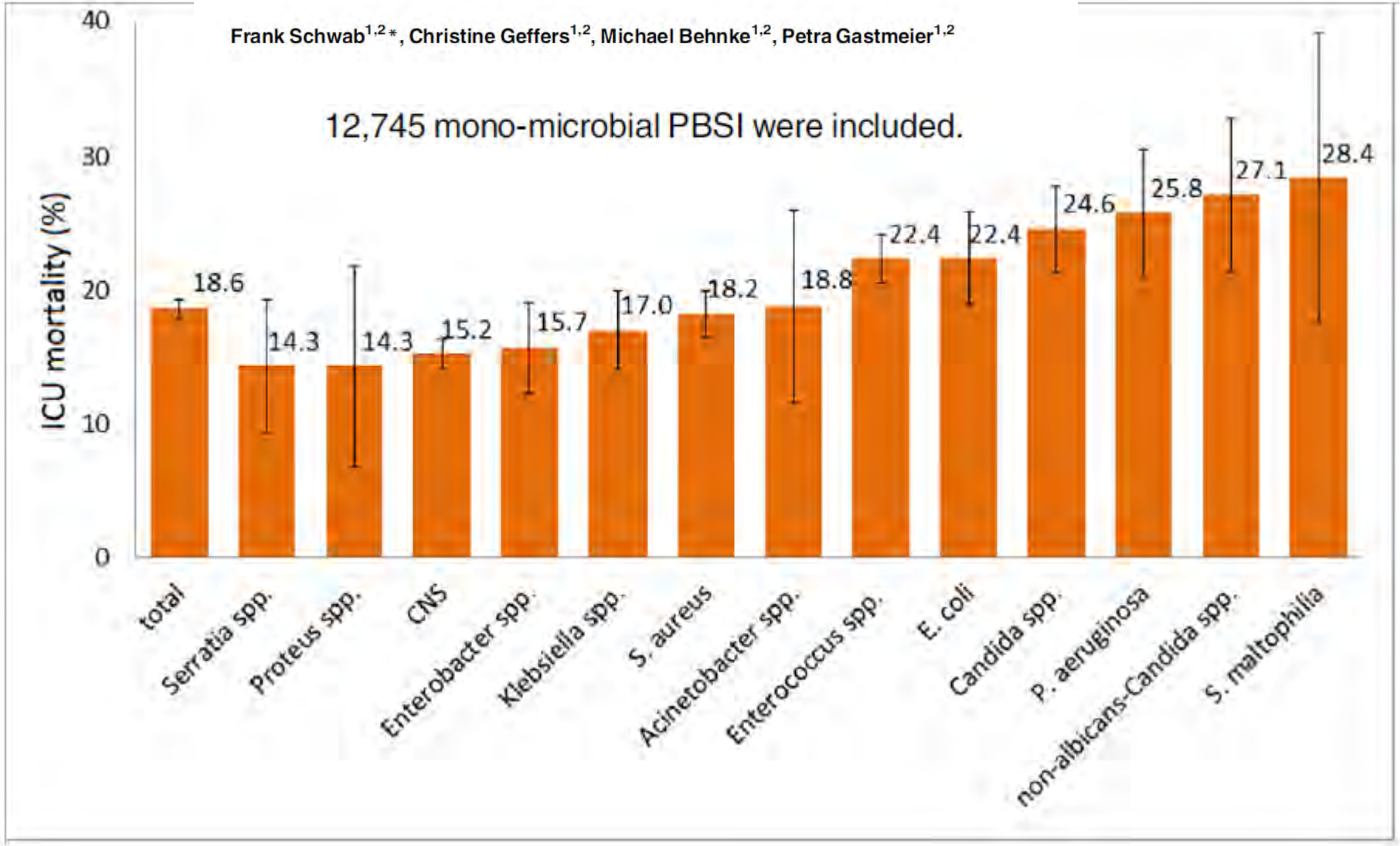
Baldesi *et al.*

RESEARCH ARTICLE

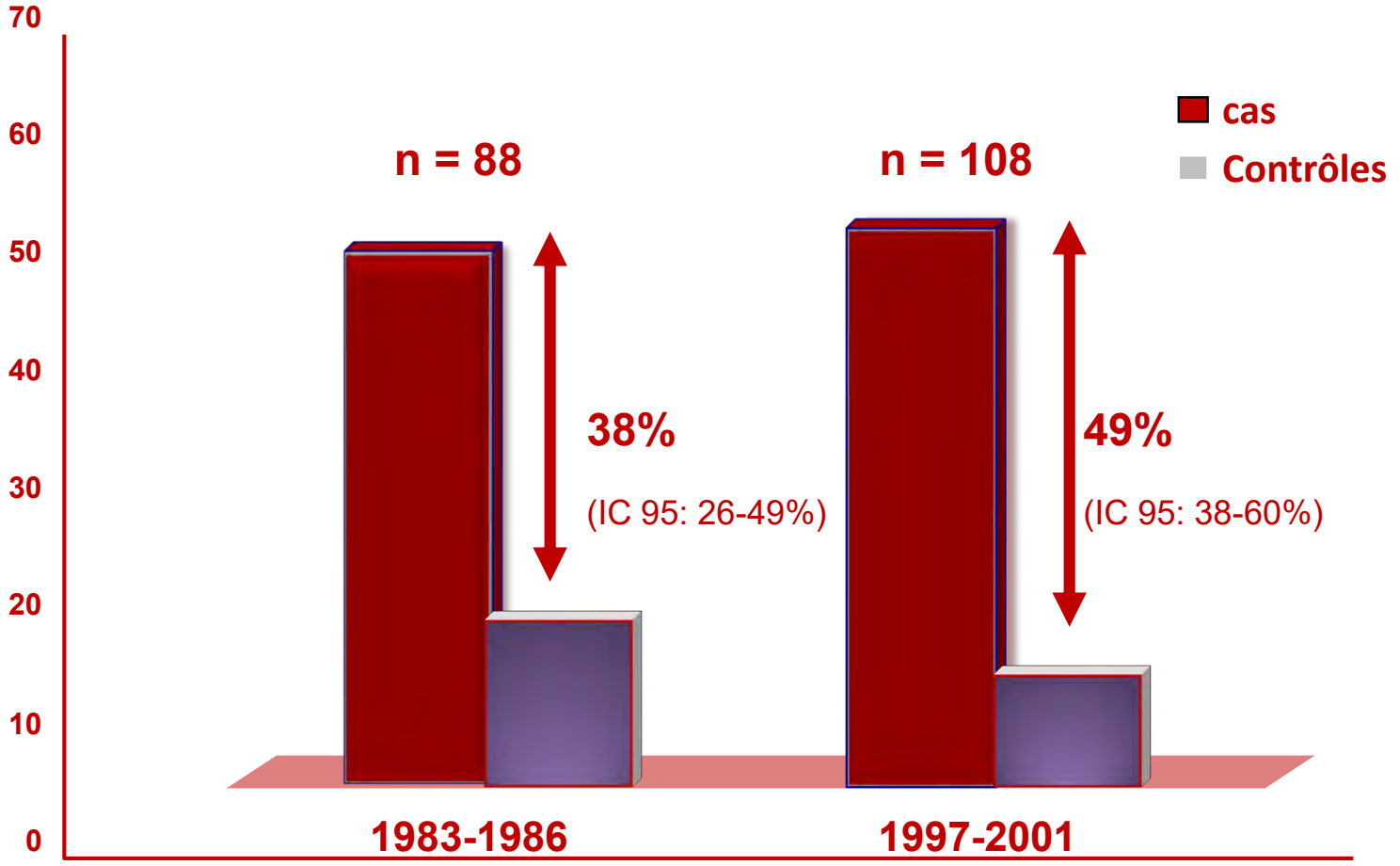
ICU mortality following ICU-acquired primary bloodstream infections according to the type of pathogen: A prospective cohort study in 937 Germany ICUs (2006-2015)

March 8, 2018

Frank Schwab[1,2]*, Christine Geffers[1,2], Michael Behnke[1,2], Petra Gastmeier[1,2]



Mortalité attribuable



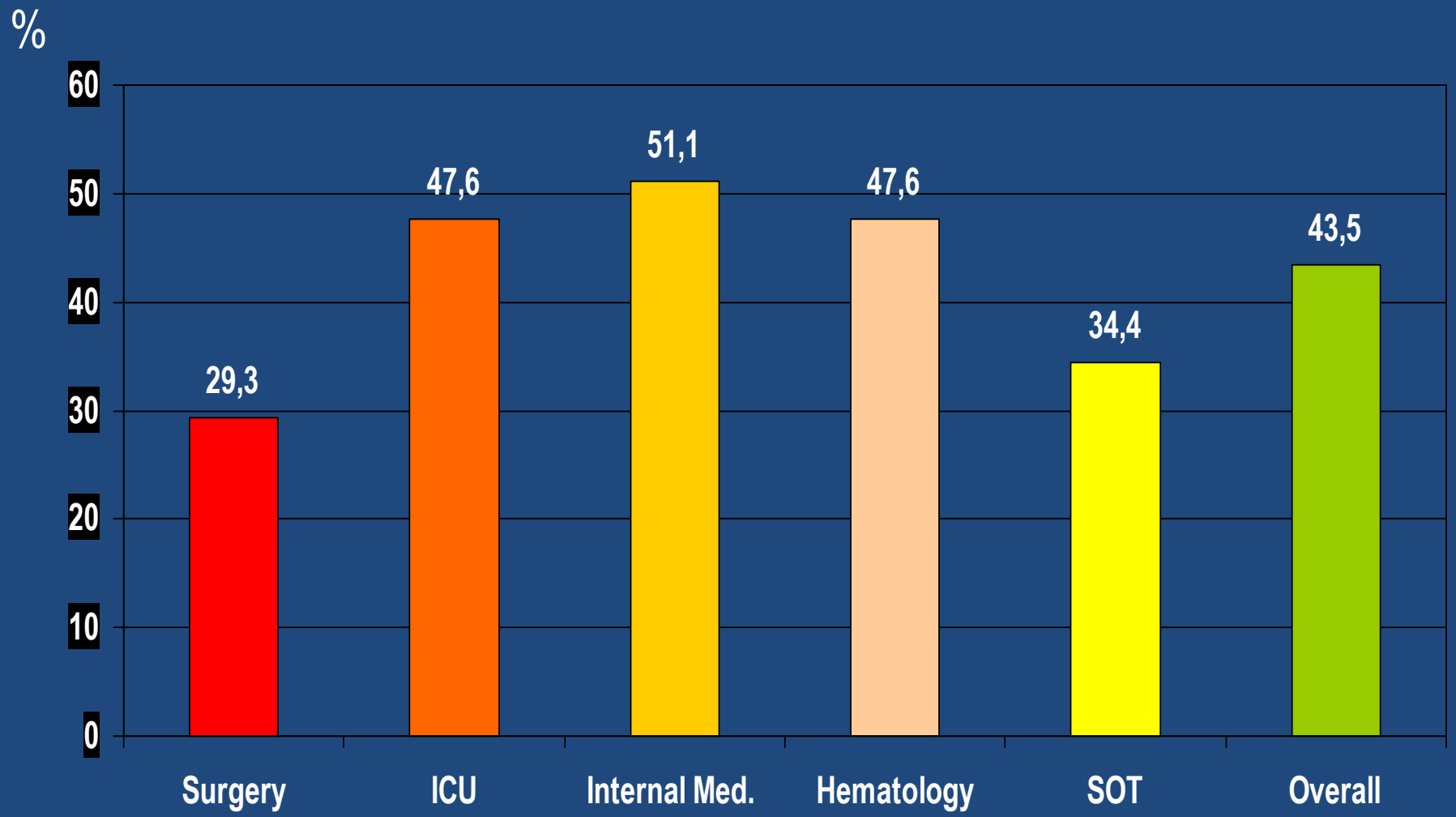
Wey Arch Intern Med 1988; 142: 2642-2645. Gudlaugsson CID 2003; 37: 1172-1177

Chocs septiques: bactériémies et fongémies acquises en réanimation

	Bactéries (n=1060)	Champignons (n=96)	p
Choc septique	45,5%	50%	NS

Paiva et coll. Crit Care 2016

Mortality from invasive *Candida* infections



Bassetti M et al. *PLoS ONE* 2011; 6(9): e24198

DOI: 10.1111/myc.13376

ORIGINAL ARTICLE

mycoses WILEY

Increasing morbidity and mortality of candidemia over one decade in a Swiss university hospital

Julien Battistolo[1] | Emmanouil Glampedakis[1,2] | Lauro Damonti[1,3] | Julien Poissy[1,4] | Bruno Grandbastien[2] | Laetitia Kalbermatter[2] | Jean-Luc Pagani[5] | Philippe Eggimann[6] | Pierre-Yves Bochud[1] | Thierry Calandra[1] | Oscar Marchetti[1,7] | Frederic Lamoth[1,8] | the Fungal Infection Network of Switzerland (FUNGINOS)

Mycoses. 2021;64:1512–1520

Caractéristiques	2004-2006, n=68	2014-2017, n=100	p
Age	59 (39-71)	68 (52-75)	<0.01
Tt immunosuppresseur	6 (9)	24 (24)	0.01
Corticoïdes	5 (7)	22 (22)	0.01
Diagnostic en réanimation	13 (19)	39 (38)	0.01
Choc septique	5 (7)	23 (23)	0.01
Infection bactérienne durant séjour	40 (59)	80 (78)	0.01
Décès hospitalier	12 (18)	33 (34)	0.03

Message 2: les candidémies en réanimation et ailleurs sont associées à un mauvais pronostic, marqueur de gravité ou mortalité attribuable?

Candidémies: les questions

1. Est-ce fréquent et quels sont les facteurs de risque?
2. Est-ce grave ?
3. Comment les diagnostiquer ?
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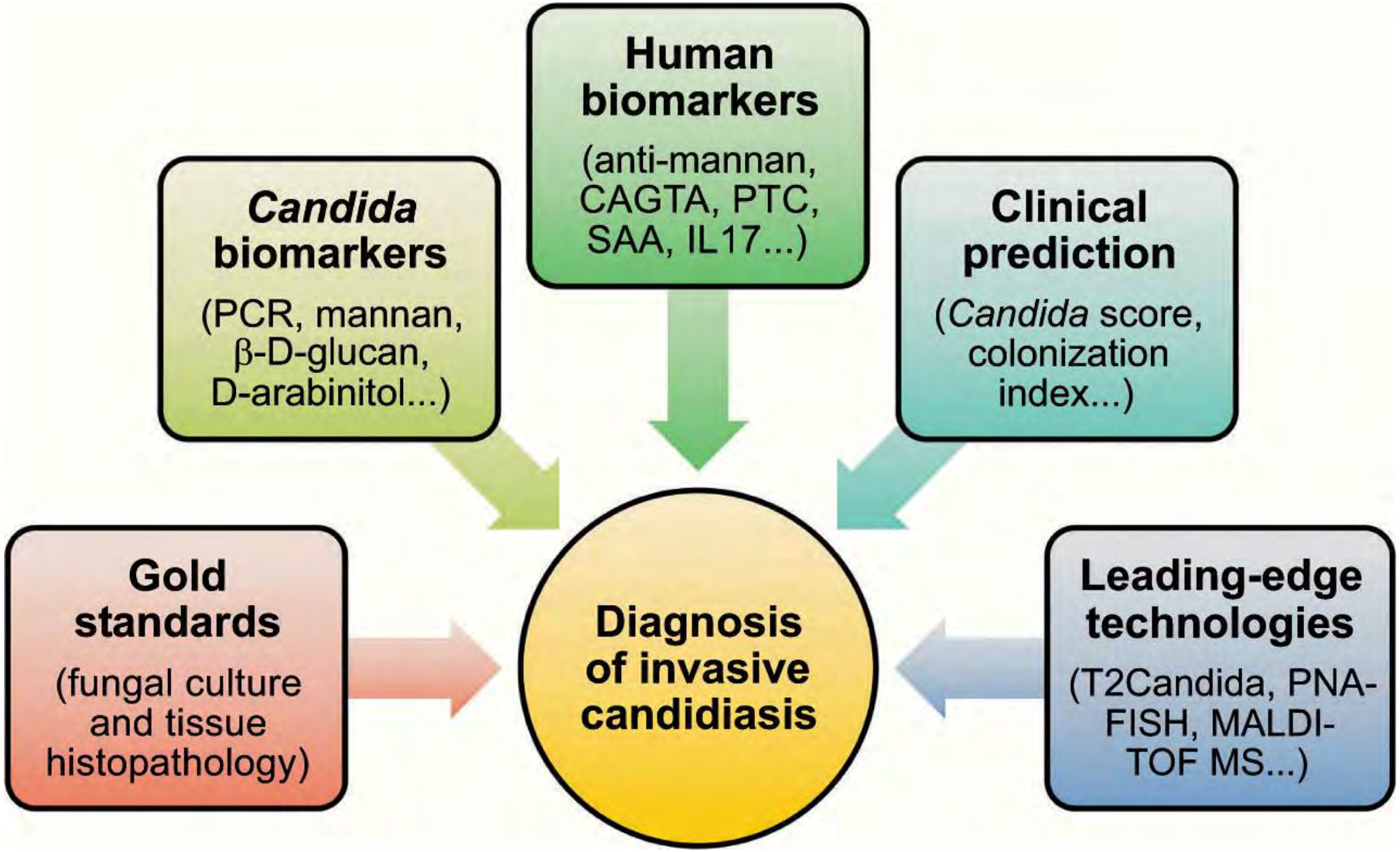
Diagnostic des candidoses invasives



- Nombre d'hémocultures recommandées = 3 (2-4) avec un volume total de sang de 40 à 60 ml pour les adultes divisés en 3 flacons aérobie et 3 flacons anaérobie de 10 ml chacun
- Les hémocultures doivent être prélevées successivement (sur 30 minutes) sur différents sites
- Durée d'incubation 5 jours

Mais faible charge fongique dans le sang

Selon les études, dans les infections à *Candida*, elles sont positives dans seulement 40% des cas d'infections profondes

Délais de pousse prolongés :

- *C albicans :* 35.3+/-18h,
- *C tropicalis :* 31+/-2h,
- *C parapsilosis* : 78+/4h
- *C glabrata :* 80+/-22h

Seulement 27% de positivité si co-infection levure/bactérie : inhibition de la croissance des levures par croissance plus rapide des bactéries et synthèse de substances antifongiques

Rôle du Maldi-TOF: identification précoce si H positive

C. Bonnal

Les critères de choix des flacons

Bactec Myco/F-lytic

- Bactec Mycosis IC/F (Labo BD®):
  - culture sélective des champignons, présence de chloramphénicol et tobramycine (antibactériens)
  - Réduction de la moitié du temps moyen de détection par rapport au milieu classique (29h versus 70h) et jusqu'à 21 versus 126 pour *C glabrata*
- Attention ! Ne pas utiliser les hémocultures Myco F Lytic (bouchon rouge) réservées aux mycobactéries

Bactec Mycosis IC/F

- BacT/Alert FAN Plus ou BacT/Alert FAN (Biomérieux®):
  - billes de polymère adsorbant pour inhiber l'action des antibiotiques/antifongiques présents dans le sang, non spécifiques des champignons (FA : aérobie, FN : anaérobie) et activer la croissance des germes.
  - Pas de flacons spéciaux pour les mycoses

BacT/Alert FAN

Fernandez J *Diagn Microbiol Infect Dis* 2009;64:402
Beyda ND *Diag Microbiol Infect Dis* 2013;77:324

C. Bonnal

Les autres sites

- Site stérile : examen direct, cultures, histologie (articulation, LCS, os, etc…)
- Cathéter
- Poumon= colonisation
- Urines= généralement colonisation
- Sites non stériles = colonisation

Candida: biomarkers and DNA detection

1,3-β-d-glucan

CAGTA*

Ag mananne
Ac anti-mannane

DNA
detection

T2 MR

Combinations

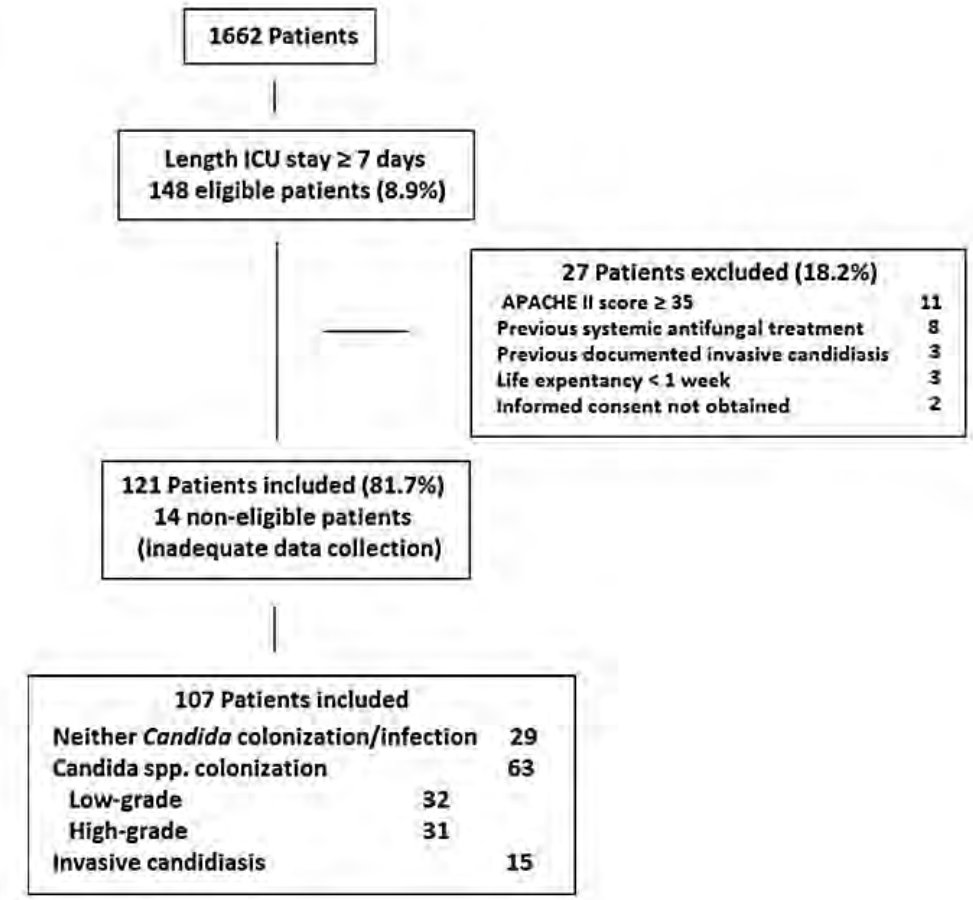
* *Candida albicans* germ tube antibodies

Intensive Care Med (2015) 41:1424–1432
DOI 10.1007/s00134-015-3922-y

ORIGINAL

Estrella Martín-Mazuelos
Ana Loza
Carmen Castro
Desirée Macías
Ismail Zakariya
Pedro Saavedra
Sergio Ruiz-Santana
Elena Marín
Cristóbal León

β-D-Glucan and *Candida albicans* germ tube antibody in ICU patients with invasive candidiasis



Discrimination between colonisation-invasive candidiasis

Table 2 Sensitivity, specificity, and positive and negative predicted values of BDG positivity for the threshold of 80 pg/mL in 89 patients who had at least two determinations

	BDG ≥80 pg/mL at least in one measurement	BDG ≥80 pg/mL in two consecutive measurements
Sensitivity (%)	80.0 (51.9–95.7)	80.0 (51.9–95.7)
Specificity (%)	44.6 (34.2–55.3)	75.7 (64.3–84.9)
Negative predictive value (%)	93.2 (82.9–94.3)	95.9 (89.3–98.5)
Positive predictive value (%)	19.0 (14.7–24.3)	34.9 (25.0–46.3)

95 % confidence intervals in parentheses

J Antimicrob Chemother 2014; **69**: 3134–3141
doi:10.1093/jac/dku225 Advance Access publication 25 June 2014

Journal of Antimicrobial Chemotherapy

Clinical validation of a multiplex real-time PCR assay for detection of invasive candidiasis in intensive care unit patients

J. Fortún[1]*, Y. Meije[1], M. J. Buitrago[2], S. Gago[2], L. Bernal-Martinez[2], J. Pemán[3], M. Pérez[4], E. Gómez-Gª Pedrosa[5], N. Madrid[1], V. Pintado[1], P. Martín-Dávila[1], J. Cobo[1], G. Fresco[1], S. Moreno[1] and M. Cuenca-Estrella[2]

Methods: We prospectively studied 63 intensive care unit patients with suspected IC and 40 healthy controls. Blood cultures and MRT-PCR were performed at day 0 and +2, +7, +14 and +21 days in all patients. In addition, β-D-glucan (BDG) and *Candida albicans* germ tube antibody (CAGTA) were quantified.

Table 2. Performance of diagnostic procedures in patients with IC, candidaemia and deep-seated candidiasis (analysis per patient)

	IC (cases, 27; population, 103)	Candidaemia (cases, 21; population, 97)	Deep-seated candidiasis (cases, 11; population, 87)	IC among highly colonized patients (Pittet index ≥0.5) (cases, 16; population, 30)
Blood culture				
sensitivity	77.7% (21/27)	—	45.4% (5/11)	87.5% (14/16)
specificity	100% (76/76)	—	100% (76/76)	100% (14/14)
PPV	100% (21/21)	—	100% (5/5)	100% (14/14)
NPV	92.7% (76/82)	—	92.7% (76/82)	87.5% (14/16)
RT-PCR				
sensitivity	96.3% (26/27)	95.2% (20/21)	90.9% (10/11)	93.7% (15/16)
specificity	97.3% (74/76)	97.3% (74/76)	97.4% (74/76)	100% (14/14)
PPV	92.8% (26/28)	90.9% (20/22)	83.3% (10/12)	100% (15/15)
NPV	98.7% (74/75)	98.7% (74/75)	98.7% (74/75)	93.3% (14/15)
BDG (≥80 pg/mL)				
sensitivity	81.5% (22/27)	95.2% (20/21)	63.6% (7/11)	81.2% (13/16)
specificity	82.9% (63/76)	85.5% (65/76)	82.9% (63/76)	50.0% (7/14)
PPV	62.8% (22/35)	64.5% (20/31)	35.0% (7/20)	65.0% (13/20)
NPV	92.6% (63/68)	98.5% (65/66)	94.0% (63/67)	70.0% (7/10)
CAGTA (≥1/160)				
sensitivity	74.1% (20/27)	71.4% (15/21)	72.7% (8/11)	75.0% (12/16)
specificity	56.5% (43/76)	53.9% (41/76)	53.9% (41/76)	35.7% (5/14)
PPV	37.7% (20/53)	30.0% (15/50)	18.6% (8/43)	57.1% (12/21)
NPV	86.0% (43/50)	87.2% (41/47)	93.2% (41/44)	55.5% (5/9)
P value				
PCR versus blood culture	Se: 0.10	—	Se: 0.06	—
PCR versus BDG	Sp: 0.004, PPV: 0.006	Sp: 0.017, PPV: 0.049	Sp: 0.005, PPV: 0.01	Sp: 0.005, PPV: 0.01
PCR versus CAGTA	Sp: <0.001, PPV: 0.001	Sp: <0.001, PPV: 0.001	Sp: <0.001, PPV: 0.001	Sp: <0.001, PPV: 0.001

Clinical Infectious Diseases

MAJOR ARTICLE

Multicenter Prospective Study of Biomarkers for Diagnosis of Invasive Candidiasis in Children and Adolescents

Brian T. Fisher,[1,2] Craig L. K. Boge,[1] Rui Xiao,[2] Sydney Shuster,[1] Dawn Chin-Quee,[3] John Allen IV,[3] Shareef Shaheen,[3] Randall Hayden,[4] Sri Suganda,[4] Theoklis E. Zaoutis,[1,2] Yeh-Chung Chang,[3] Dwight E. Yin,[5] Anna R. Huppler,[6] Lara Danziger-Isakov,[7] William J. Muller,[8] Emmanuel Roilides,[9] José Romero,[10] Paul K. Sue,[11] David Berman,[12] Rachel L. Wattier,[13] Natasha Halasa,[14] Alice Pong,[15] Gabriela Maron,[16] Pere Soler-Palacin,[17] Susan C. Hutto,[18] Blanca E. Gonzalez,[19] Christine M. Salvatore,[20] Sujatha Rajan,[21] Michael Green,[22] Elizabeth Doby Knackstedt,[23] Sarmistha B. Hauger,[24] and William J. Steinbach[3]

Table 7. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value for the T2Candida and Platelia *Candida* Antigen Plus Results Used in Combination

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Specimens Exceeding Cutoff
Test	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	n
T2Candida only	77.3 (54.6, 92.2)	97.2 (95.1, 98.6)	60.7 (40.6, 78.5)	98.7 (97.0, 99.6)	28
Platelia *Candida* Antigen Plus only	40.9 (20.7, 63.7)	97.2 (95.1, 98.6)	45.0 (23.1, 68.5)	96.7 (94.5, 98.3)	20
At least one test positive	86.4 (65.1, 97.1)	94.7 (92.0, 96.7)	47.5 (31.5, 63.9)	99.2 (97.7, 99.8)	40
Both tests positive	31.8 (13.9, 54.9)	99.8 (98.6, 100.0)	87.5 (47.4, 99.7)	96.3 (94.0, 97.9)	8

418 specimen pairs (406 enrolled, 12 spikes) included in analysis, 22 specimens with event (5.3%).

En ligne janvier 2022

Diagnosis – Microbiology – Antigen Detection

Population	Intention	Intervention	SoR	QoE	Reference	Annotation
ICU patients with suspected Candida infection	To support the decision to treat	Determine serum BDG (Fungitell) before treatment initiation & reassess based on result	A	IIu	Prattes Mycoses 2014 Nucci JAC 2016 Posteraro JAC 2016	N=66 N=85 N=198
ICU patients	To diagnose invasive candidiasis	Serum BDG (Fungitell)	A/B	IIr	Hanson PlosOne 2012 Lamoth CID 2012 Karageorgopoulos CID 2011	N=64

Diagnosis – Microbiology – Antigen Detection

Population	Intention	Intervention	SoR	QoE	Reference
ICU patients	To differentiate candidemia from bacteremia	Serum BDG (Fungitell) plus Procalcitonin	B	III	Giacobbe CritCare 2017
Hospitalized patients	To diagnose candidemia	BDG (Wako)	C	III	Friedrich JCM 2012
Hospitalized patients	To diagnose candidemia	Automated BDG (Fungitell)	B	III	Prüller MedMycol 2014
ICU patients post intestinal surgery	To diagnose invasive candidiasis	Serum BDG (Fungitell)	C	III	Szyszkowitz OFID 2019
Hematologic malignancy	To detect Candida infection early	Screening for mannan	C	III	Duettmann Mycoses 2016 Miluska CritCare 2010 Verduyn-Lunel MedMycol 2011
ICU, hem, cancer patients	To diagnose invasive candidiasis	Mannan and anti-mannan	B/C	II	Mikulska CritCare 2010 Verduyn-Lunel MedMycol 2011 Duettmann Mycoses 2016

Message 3: le diagnostic de candidose invasive repose d'abord sur les hémocultures, la culture d'un site stérile. Le dosage du β-D-glucan peut aider

Candidémies: les questions

1. Est-ce fréquent et quels facteurs de risque?
2. Est-ce grave ?
3. Comment les diagnostiquer ?
4. Quand traiter?
5. Comment traiter ?

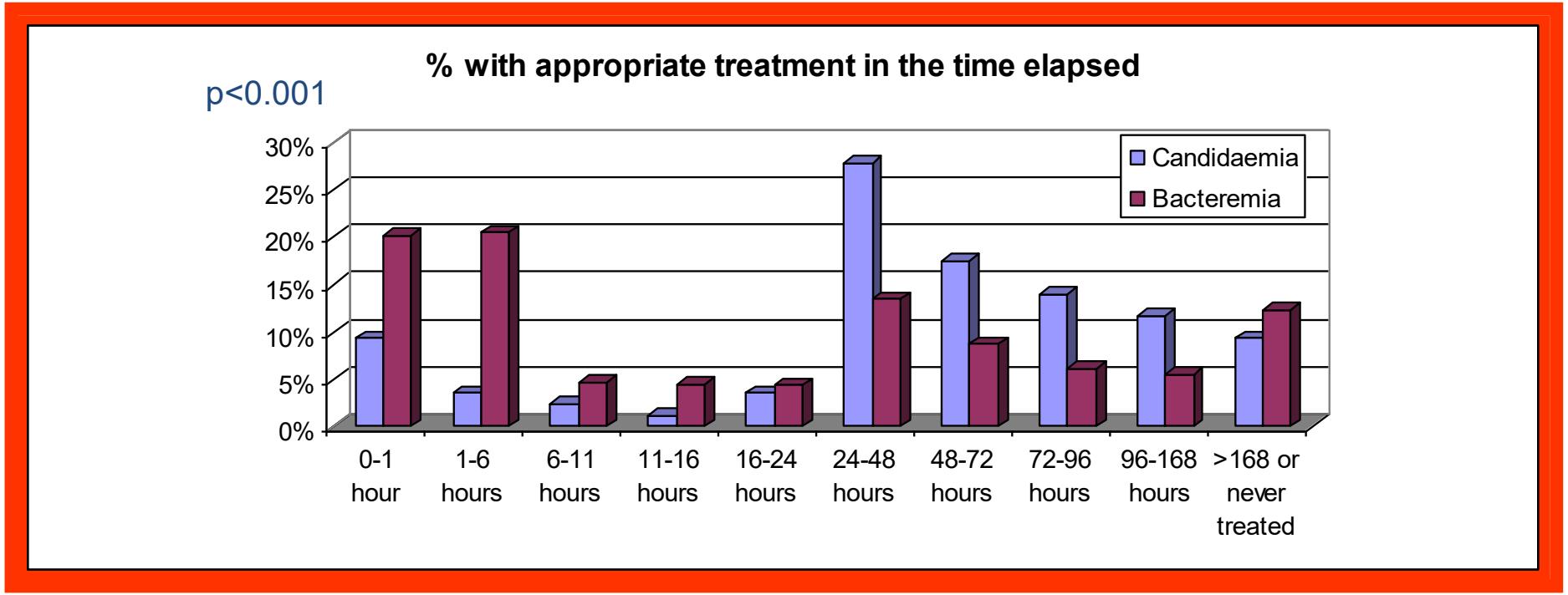
2 strategies

Traitement antifongique sur candidose invasive documentée

Traitement antifongique probabiliste

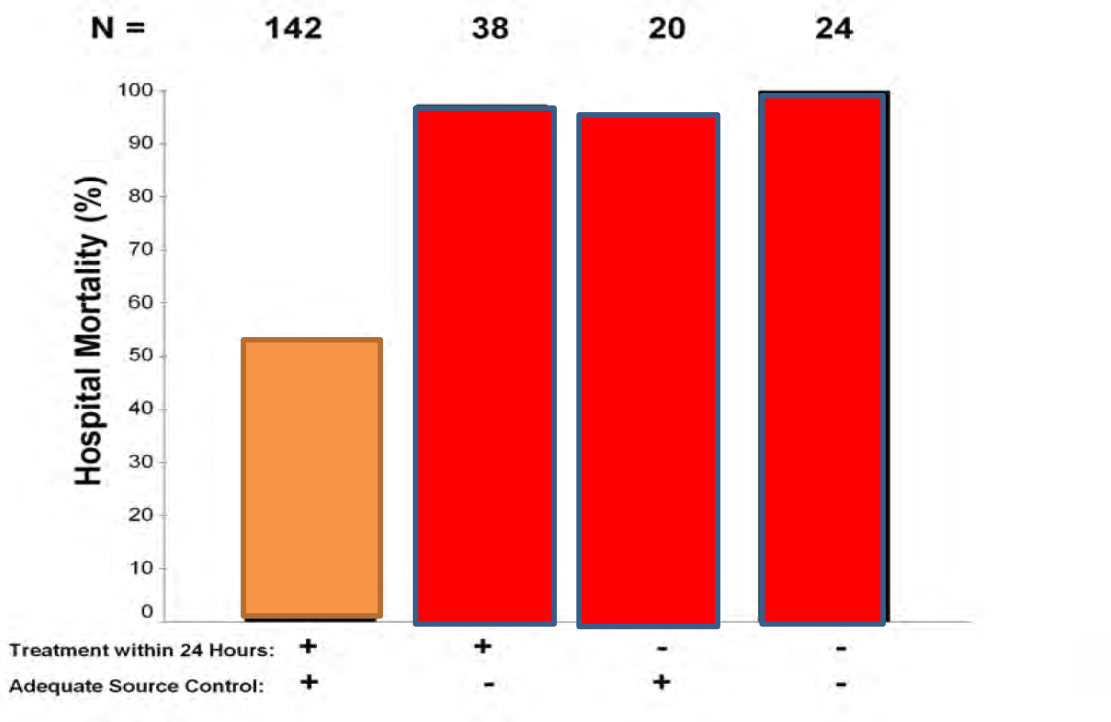
Candidaemia is treated later than bacteraemia

Eurobact



Tabah A, et al. Intensive Care Med 2012;38:1930–45 and personal data

Candida septic shock: role of early AFT and source control



Kollef M et al. *Clin Infect Dis.* 2012 Jun;**54**(12):1739-46

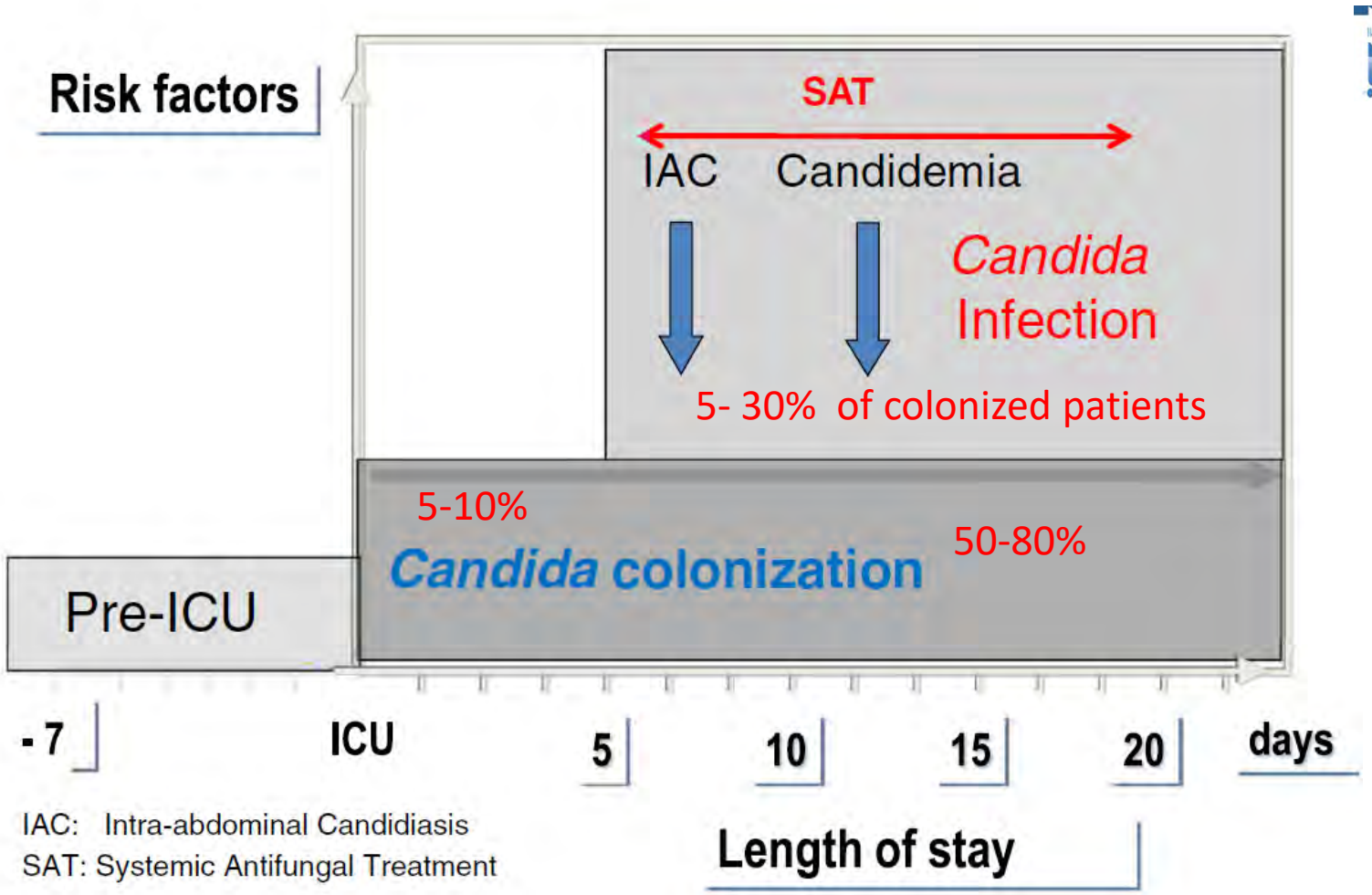
Clinical Infectious Diseases
IDSA GUIDELINE

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David R. Andes,[3] Cornelius J. Clancy,[4] Kieren A. Marr,[5] Luis Ostrosky-Zeichner,[6] Annette C. Reboli,[7] Mindy G. Schuster,[8] Jose A. Vazquez,[9] Thomas J. Walsh,[10] Theoklis E. Zaoutis,[11] and Jack D. Sobel[12]

28. Empiric antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever and should be based on clinical assessment of risk factors, surrogate markers for invasive candidiasis, and/or culture data from nonsterile sites *(strong recommendation; moderate-quality evidence)*. Empiric antifungal therapy should be started as soon as possible in patients who have the above risk factors and who have clinical signs of septic shock *(strong recommendation; moderate-quality evidence)*.

Tout est dans la colonisation?



From Leon C et al. ICM 2014

Clinical scores : Yes but…

Table 2 Comparison of invasive candidiasis prediction rules

Score, year	Patients (*n*) type of study	ICUs	Sensitivity (95 % CI)	Specificity (95 % CI)	PPV (95 % CI)	NPV (95 % CI)	Threshold
Colonization index, 1994 [46]	29 prospective	1	100	66.6 (43–83)	64.7 (41–83)	100	≥0.5
Dupont score, 2003 [54][a]	57 prospective	1	84	50	67	72	≥3
Candida score, 2006 [39]	1,699 retrospective	73	81 (69–89)	74 (70–77)	24.6 (19–31)	97.4 (95–98)	≥ 3
Candida score, 2009 [55]	1,107 prospective	36	77.6 (65–86)	66.2 (63–69)	13.8 (10–17)	97.7 (96–98)	≥3
Ostrosky rule, 2011 [56]	597 retrospective	6	90 (72–97)	48 (44–52)	6 (4–9)	99 (97–99)	MV + BSA + CVC + other

ICU intensive care unit, *MV* mechanical ventilation, *BSA* broad-spectrum antibiotics, *CVC* central venous catheter

[a] Grade C

From Leon C et al. ICM 2014

Poissy et al. Critical Care (2020) 24:109
https://doi.org/10.1186/s13054-020-2766-1

Critical Care

RESEARCH Open Access

Risk factors for candidemia: a prospective matched case-control study

Intensive-care unit score (N=255)	
A1	
Risk Factor	Points
Total parenteral nutrition	+2.5
Acute kidney failure	+1.5
Heart disease	+1.5
Previous septic shock	+1.0
Aminoglycoside	+1.0

Non-intensive-care unit score (N=348)	
B2	
Risk Factor	Points
Central venous catheter	+2.5
Nitroimidazole	+1.0
Total parenteral nutrition	+1.0
Glycopeptide	+1.0

Se optimale : $\geq$ 4: Se:69%, Sp: 70%
Sp optimale : $\geq$ 5: Se:43%, Sp: 88%

Se optimale : $\geq$ 2: Se: 83%, Sp:49%
Sp optimale : $\geq$ 4: Se: 51%, Sp:81%

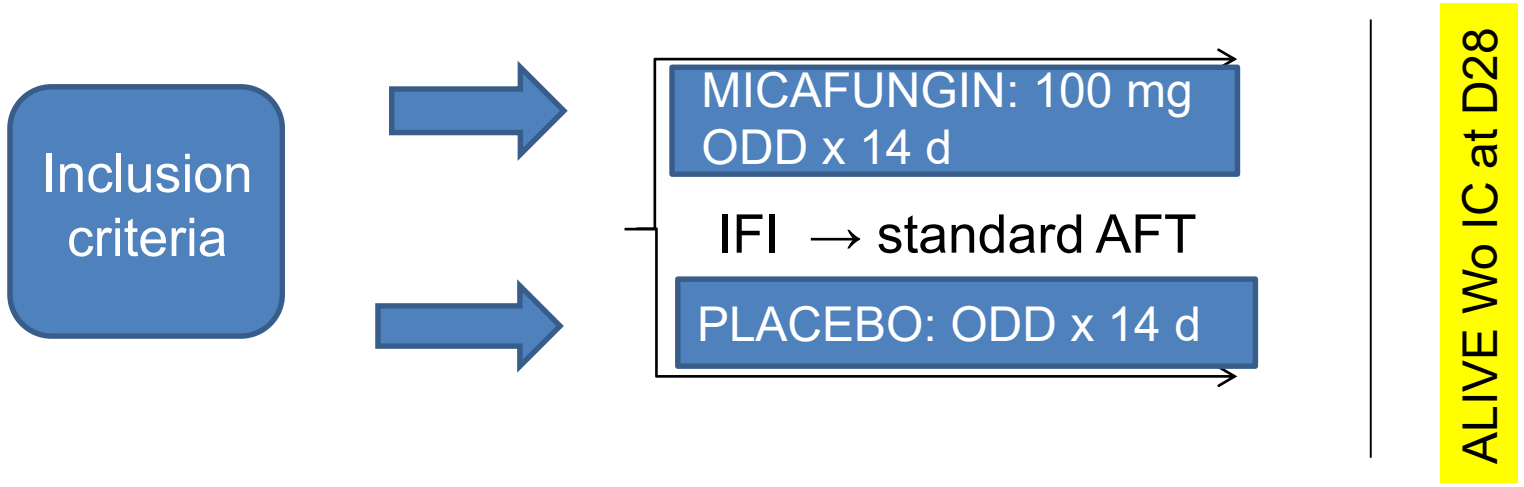
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, *Candida* Colonization, and Multiple Organ Failure
The EMPIRICUS Randomized Clinical Trial

October 5th 2016

Jean-Francois Timsit, MD, PhD; Elie Azoulay, MD, PhD; Carole Schwebel, MD, PhD; Pierre Emmanuel Charles, MD, PhD; Muriel Cornet, PhamD; Bertrand Souweine, MD, PhD; Kada Klouche, MD, PhD; Samir Jaber, MD, PhD; Jean-Louis Trouillet, MD, PhD; Fabrice Bruneel, MD; Laurent Argaud, MD, PhD; Joel Cousson, MD; Ferhat Meziani, MD, PhD; Didier Gruson, MD, PhD; Adeline Paris, PharmD; Michael Darmon, MD, PhD; Maité Garrouste-Orgeas, MD, PhD; Jean-Christophe Navellou, MD; Arnaud Foucrier, MD; Bernard Allaouchiche, MD, PhD; Vincent Das, MD; Jean-Pierre Gangneux, PharmD, PhD; Stéphane Ruckly, MSc; Daniele Maubon, MD, PhD; Vincent Jullien, PharmD; Michel Wolff, MD, PhD; for the EMPIRICUS Trial Group

Main end-point

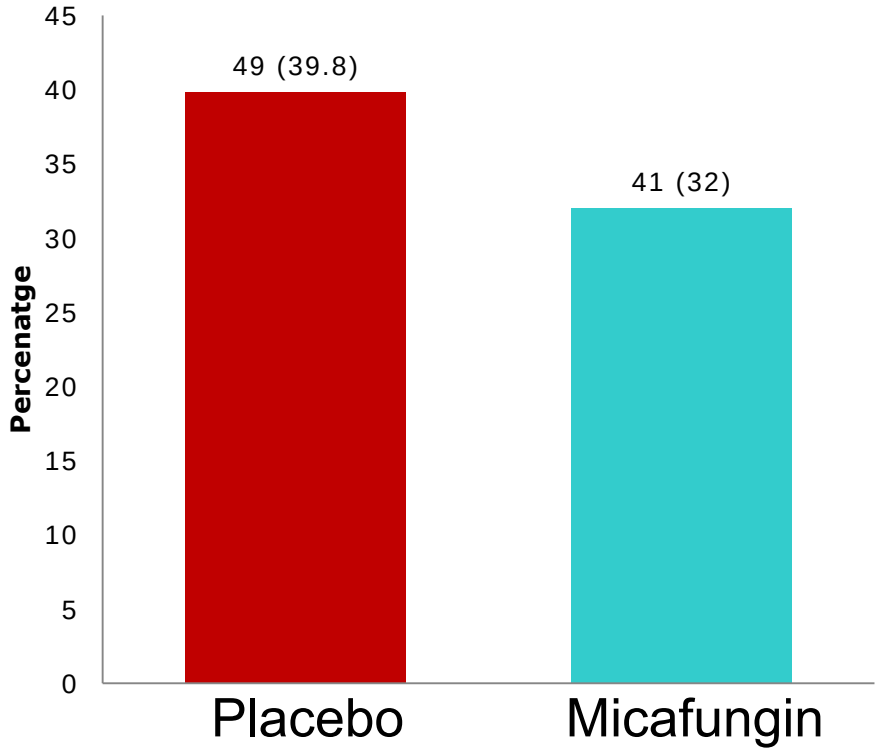


- ICU ≥ 5 d, - Sepsis, - Mechanical ventilation ≥ 4 d, - CVKT
- ATB ≥ 4 d previous week, - ≥ 1 extra-digestive site colonized with *Candida* sp, -If concomitant bacterial infection: appropriate ATB, - ≥ 1 organ failure (SOFA ≥ 2)

Candida colonization at inclusion

Candida colonization	Micafungin (n=128)	Placebo (n=123)
n positive sites	3.1±1.3	3.3±1.4
Tracheal, n (%)	102 (80)	99 (80.5)
Oropharyngeal, n (%)	98 (77)	101 (82)
Rectal, n (%)	81 (63)	74 (60)
Cutaneous, n (%)	58 (45)	62 (50)
Urinary, n (%)	41 (32)	40 (32.5)
Other, n (%)	16 (12.5)	22 (18)

Primary endpoint: death or IC at D28



***HR = 0.74 [0.48 ; 1.15], p=0.1858**

* Cox model stratified by center and adjusted to imbalances at inclusion

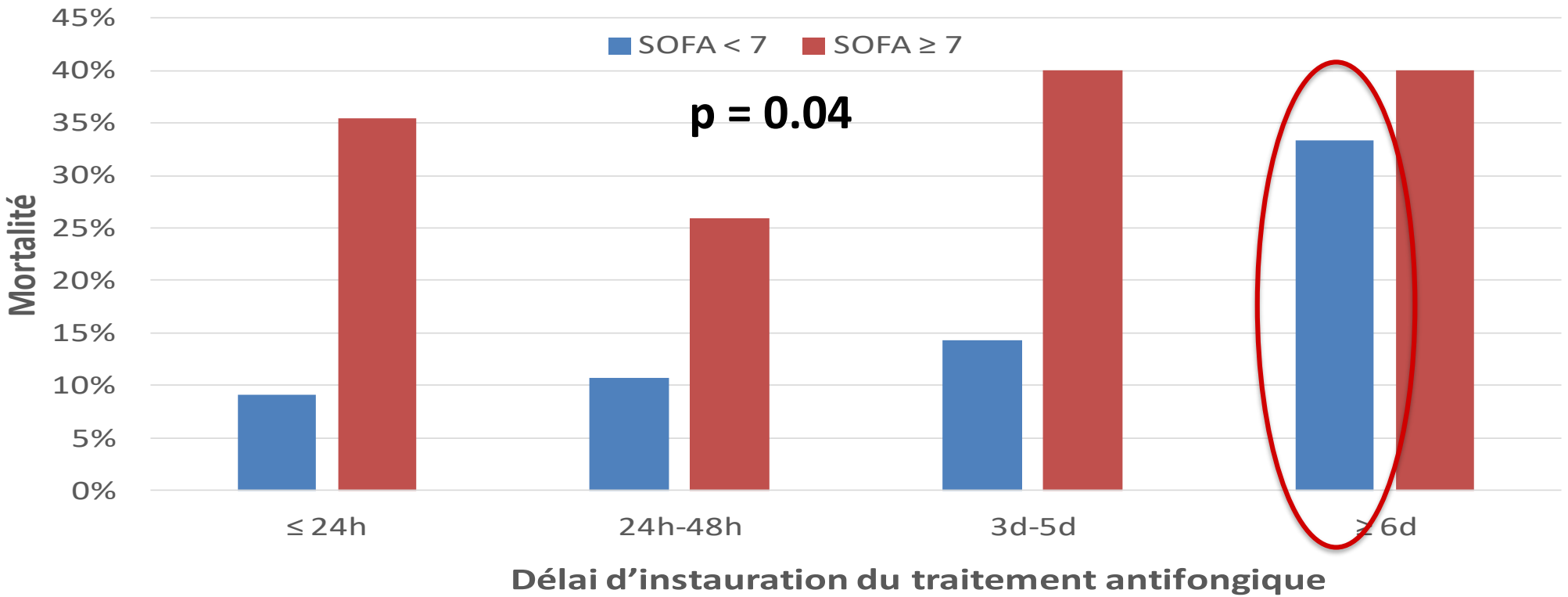
Péritonites avec *Candida*: de quoi parlons nous?

Table 1 Guide for selection of the study populations and explanations for heterogeneity of published series

Medical history	Underlying diseases	Acquisition	Clinical situation	Severity	Management
Surgical wards	No underlying disease	Community-acquired	Primary peritonitis	No sign of severity	Empirical therapy
ICU	Solid transplant	Hospital-acquired	Secondary peritonitis	Septic shock	Adequacy of:
Medical wards	Cirrhosis	Health-care associated	Tertiary peritonitis	High severity scores	- Antifungal treatment
	Steroid therapy		Pancreatitis		- Antibacterial treatment
	Neutropenia		Biliary tract infection		- Source control
	Other causes of immunosuppression				• Surgical site
	Solid tumor				• Central catheter

Impact pronostique du délai entre prélèvement et début du traitement antifongique en fonction du SOFA

N=159 péritonites avec Candida prouvée (amarcand2)



La précocité ou le retard d'instauration du traitement antifongique n'impactent la mortalité que chez les malades les moins sévères (SOFA < 7) et pour des retards d'au moins 6 jours (p = 0.04)

Montravers P CMI 2016

Candida as a risk factor for mortality in peritonitis*

Philippe Montravers, MD, PhD; Hervé Dupont, MD, PhD; Remy Gauzit, MD; Benoit Veber, MD; Christian Auboyer, MD; Patrick Blin, MD, MSc; Christophe Hennequin, MD, PhD; Claude Martin, MD

Univariate and multivariate analysis with regard to deaths of patients with nosocomial peritonitis (n = 164)

	Univariate Analysis		Multivariate Analysis	
Risk Factors	Odds Ratio (95% CI)	p Value	Adjusted Odds Ratio (95% CI)	p Value
Case group	2.4 (1.2–4.6)	.01	3.0 (1.3–6.7)	.009
Upper gastrointestinal tract site	2.1 (1.1–4.1)	.02	4.9 (1.6–14.8)	.005
Empirical antifungal treatment	1.9 (0.9–3.9)	.07	—	—
Inappropriate empirical antibiotic treatment	2.2 (1.1–4.3)	.02	1.6 (0.6–4.3)	.3

- « Death occurred in 17 of the 33 (52%) patients who received empirical antifungal treatment, whereas 11 of the 25 (44%) patients initially untreated patients died. »
- « Similarly, 23 of the 46 (50%) patients who received antifungal treatment after identification of *Candida* species died vs. five of the 12 (42%) untreated cases. »

La présence de levures est associée au pronostic (Uniqt Perit. nosocomiale) mais, ni le traitement empirique, ni le traitement secondaire ne modifie le pronostic!!

Crit Care Med 2006; 34:646–652

SEVEN-DAY PROFILE PUBLICATION

ESICM/ESCMID task force on practical management of invasive candidiasis in critically ill patients

Intensive Care med 2019; Jun;45(6):789-805

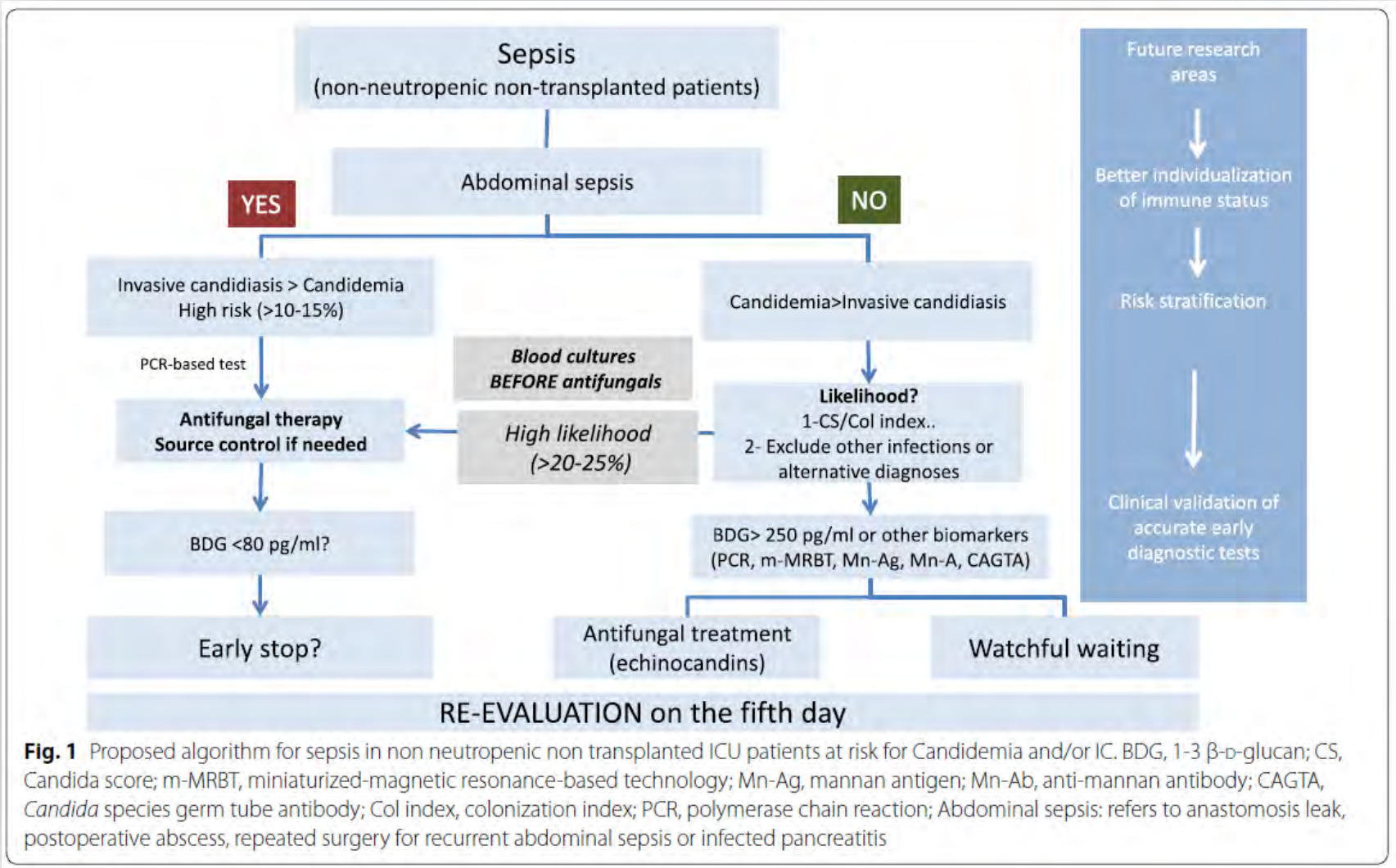


Fig. 1 Proposed algorithm for sepsis in non neutropenic non transplanted ICU patients at risk for Candidemia and/or IC. BDG, 1-3 β-D-glucan; CS, Candida score; m-MRBT, miniaturized-magnetic resonance-based technology; Mn-Ag, mannan antigen; Mn-Ab, anti-mannan antibody; CAGTA, *Candida* species germ tube antibody; Col index, colonization index; PCR, polymerase chain reaction; Abdominal sepsis: refers to anastomosis leak, postoperative abscess, repeated surgery for recurrent abdominal sepsis or infected pancreatitis

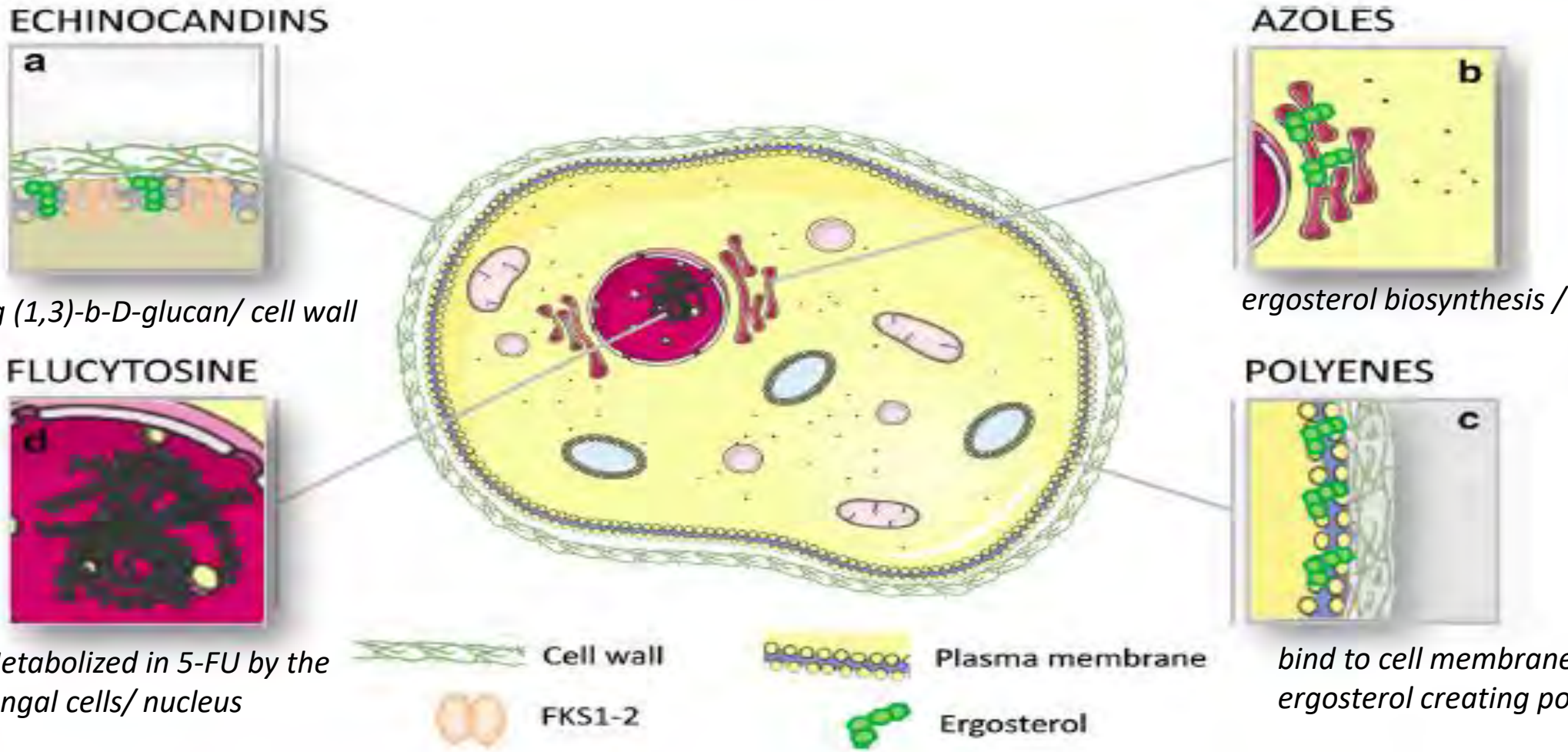
Message 4:

- Traiter dès la première hémoculture positive ou site stérile
- Si choc septique + FDR + multicolonisation: à discuter
- Péritonites: selon risque et levures à l'examen direct

Candidémies: les questions

1. Est-ce fréquent ?
2. Est-ce grave ?
3. Comment les diagnostiquer ?
4. Quand traiter?
5. Comment traiter ?

Antifungals: mode of action



inhibiting (1,3)-b-D-glucan/ cell wall

ergosterol biosynthesis / cell membrane

Metabolized in 5-FU by the fungal cells/ nucleus

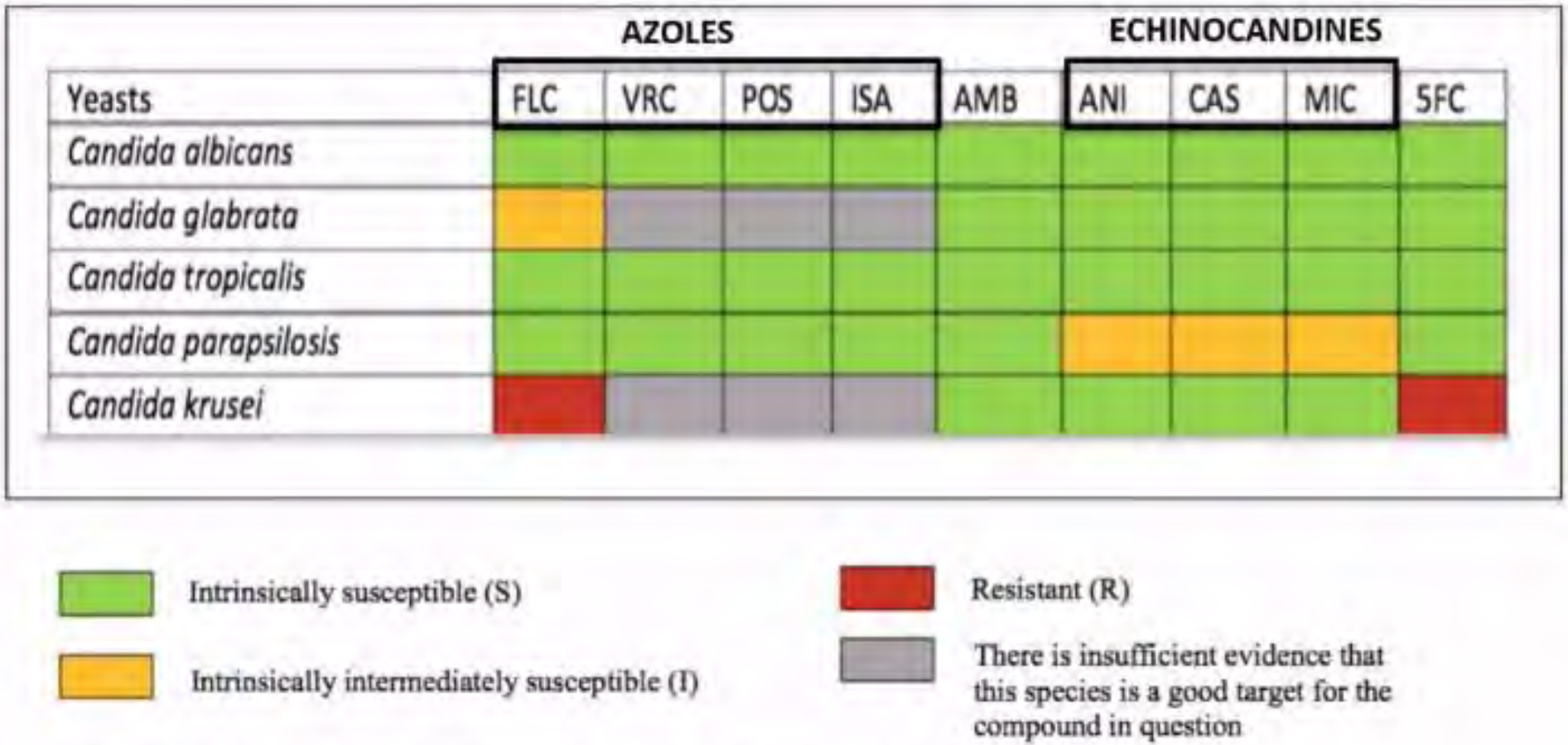
bind to cell membrane ergosterol creating pores

D Maubon, Intensive Care Med (2014) 40:1241–1255

PK

	Oral	Half-life(H)	Half life ICU	Elimination	CSF/brain
Fluconazole	+++	25-40	30-70	Renal	Good
Voriconazole	+++	7	10	liver	Good
Posaconazole	++	90	?	Liver, Feces	Good?
Isavuconazole	+++	100-130	??	Liver, Feces	Good?
AmphoB Deox	-	24-98	30	20% Biliary	Low
AmphoB L	-	6,8	15	20 % Urinary	> AmB D
Flucytosine	+	4		Renal	Good
Echinocandins	-	15	10-15	Extra Renal	Low

Spectre de sensibilité naturelle aux antifongiques



Morio et coll., Internationnal Journal of Antimicrobial Agents 2017

Diapositive E. Bougnoux RICAI janvier 2020

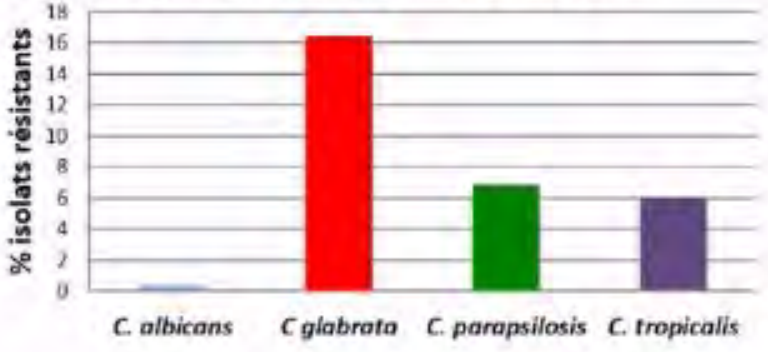
Résistances ????

En France : Candidémie 2004-2018 : 5196 isolats
Proportion d'isolats de *Candida* résistants selon les seuils EUCAST

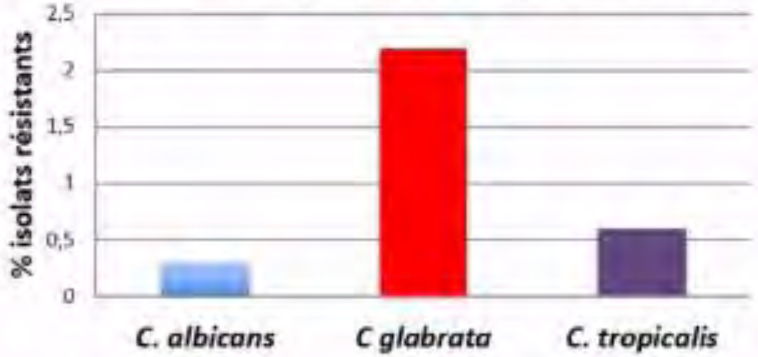
	Fluconazole		Voriconazole		Caspofungine	
Espèces	Seuil mg/L	% R [extrêmes]	Seuil mg/L	% R [extrêmes]	Seuil mg/L	% R [extrêmes]
C. albicans	> 4	**0,4 %** [0 - 1,2]	> 0,25	**0,5 %** [0 – 2,4]	> 0,25	**0,3 %** [0 – 1,8]*
C. glabrata	> 32	**16,5 %** [2 - 28,3] *#	-	-	> 0,25	**2,2 %** [0 – 7,3]
C. parapsilosis	> 4	**6,9 %** [0 – 18,9] *	> 0,25	**2,5 %** [0 – 6,8]	-	
C. tropicalis	> 4	**6,1 %** [0 - 15,6] *#	> 0,25	**8,9 %** [0 - 27,8]*#	> 0,25	**0,6 %** [0 - 3,4]

Rapport CNRMA 2018

16% *C. glabrata* R Fluconazole



2,2% *C. glabrata* R Caspofungine

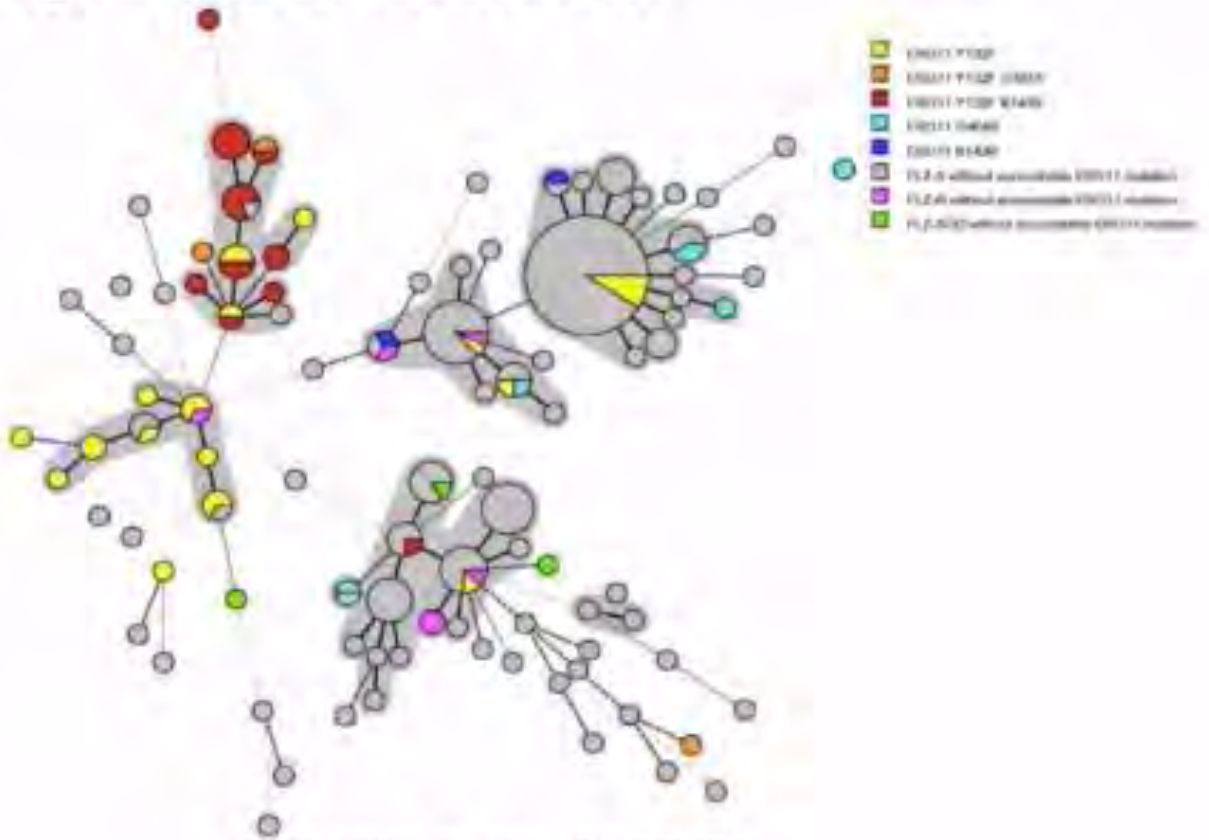


Diapositive: ME Bougnoux RICAI2020

Emergence chez *C. parapsilosis* de souches clonales résistantes au fluconazole

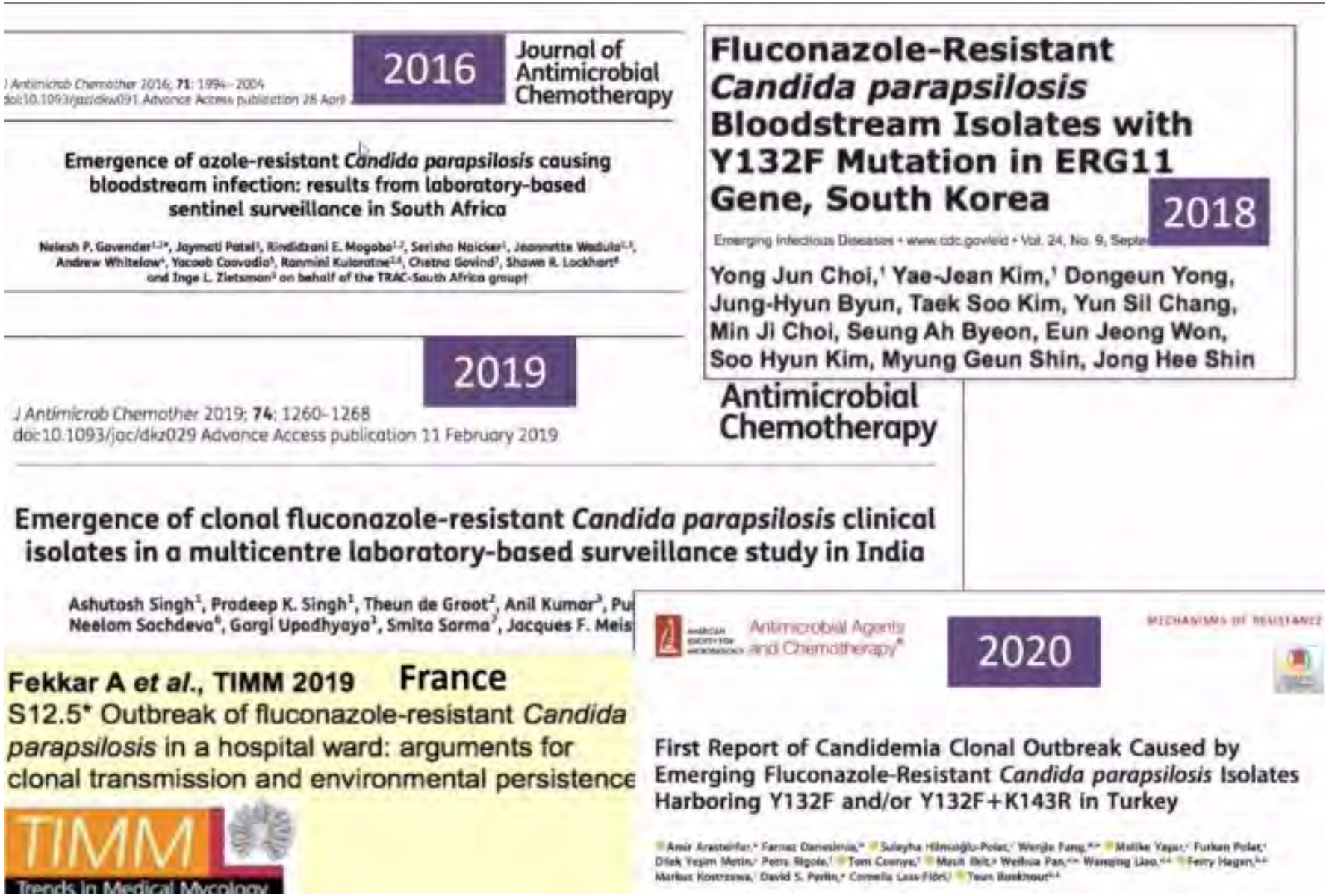
Prédominance de Erg11 **Y132F et K143R**

- USA
- Brésil
- Italie
- Koweït
- Corée du sud
- Inde
- Afrique du sud
- Turquie



Arafthefar et coll, AAC 2020

Diapositive: ME Bougnoux, RICAI 2020



Diapositive: ME Bougnoux, RICAI 2020

Emergence multifocale en Asie de souches clonales fluconazole R chez *Candida tropicalis*

- Chine, Taiwan, Singapour….
- Taux de prévalence : 15 - 45% (CMI ≥ 8 mg/L)
- Mécanismes de résistance plus complexes : surexpression de Erg11p, mutation Erg11 Y132F, pompe à efflux
- Patients naifs dans >50% des cas
- Hypothèse : transfert horizontal par l'environnement/ agriculture/ cultures (fruits)

Fan et coll., Front Microbiol. 2017; TeoJQ et coll., BMC Infect Dis. 2019 ; Zhou ZL et coll., Diagn MicrobiolInfect Dis. 2016 ; Tan et coll., Med Mycol. 2016 ; PY Chen et coll., Emerging Inf Dis 2019

Diapositive : ME Bougnoux RICAI 2020

Résistance aux Echinocandines chez *Candida albicans* et *Candida glabrata*

- Pré-exposition aux échinocandines (principal FR*)
- Délai d'apparition médian assez long : 2-4 semaines d'exposition
- Mutations connues

conférant R chez *C. albicans* et *C. glabrata*

*Shields et coll., AAC 2015;
Beyda et coll, CID 2014
Coste et coll., Infection 2020

Emerging echinocandin-resistant *Candida albicans* and *glabrata* in Switzerland J Infection2020

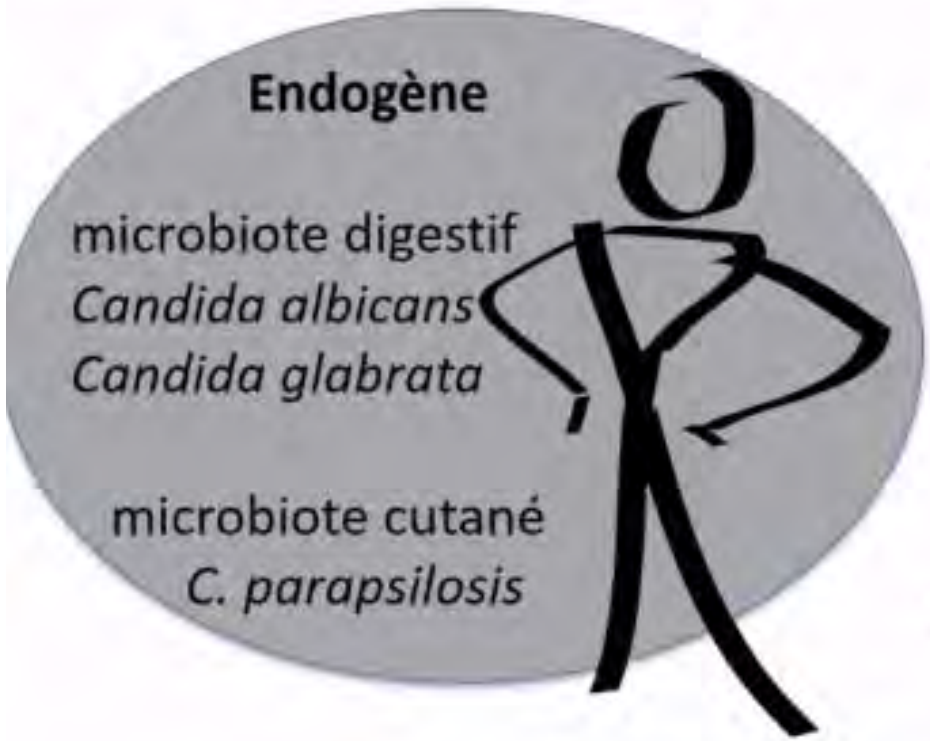
A. T. Coste[1] · A. Kritikos[2] · J. Li[1,2] · N. Khanna[3] · D. Goldenberger[4] · C. Garzoni[5] · C. Zehnder[6] · K. Boggian[7] · D. Neofytos[8] · A. Riat[9] · D. Bachmann[1] · D. Sanglard[1] · F. Lamoth[1,2] on behalf of The Fungal Infection [Network] Switzerland (FUNGINOS)

9 épisodes de candidemie :
souches R aux candines (RX) après exposition à la caspofungine n=7 ou à l'anidulafongine n=2

Cases	Species	Episode	MIC µg/mL (CLSI classification)*				FKS hotspot mutations**			
			AND	MCF	CSP	FLC	*FKS1*		*FKS2*	
							HS1	HS2	HS1	HS2
1	*C. albicans*	1st	0.25 (S)	0.125 (S)	0.5 (I)	4 (SDD)	–	–	na	
		2nd	**2 (R)**	**2 (R)**	**4 (R)**	**4 (SDD)**	**S645P**	–		
2	*C. albicans*	1st	**2 (R)**	**4 (R)**	**8 (R)**	**2 (S)**	**S645P**	–		
3	*C. albicans*	1st	**2 (R)**	**4 (R)**	**>16 (R)**	**<0.5 (S)**	**S645P**	–		
4	*C. albicans*	1st	**2 (R)**	**1 (R)**	**1 (R)**	**<0.5 (S)**	–	**R1361G**		
5	*C. glabrata*	1st	**2 (R)**	**4 (R)**	**>16 (R)**	**4 (SDD)**	–	–	**S663P**	–
6	*C. glabrata*	1st	**4 (R)**	**4 (R)**	**16 (R)**	**4 (SDD)**	–	–	**F659_**	–
7	*C. glabrata*	1st	0.25 (I)	0.06 (S)	0.25 (I)	1 (SDD)	–	–	–	–
		2nd	**4 (R)**	**4 (R)**	**>16 (R)**	**1 (SDD)**	–	–	**S663P**	–
8	*C. glabrata*	1st	0.12 (S)	0.015 (S)	0.06 (S)	8 (SDD)	–	–	–	–
		2nd	**4 (R)**	**4 (R)**	**>16 (R)**	**4 (SDD)**			**S663P**	
9	*C. glabrata*	1st	0.015 (S)	0.015 (S)	0.03 (S)	4 (SDD)	–	–	–	–
		2nd	**0.25 (I)**	**4 (R)**	**16 (R)**	**8 (SDD)**	**S629P**	–	–	–

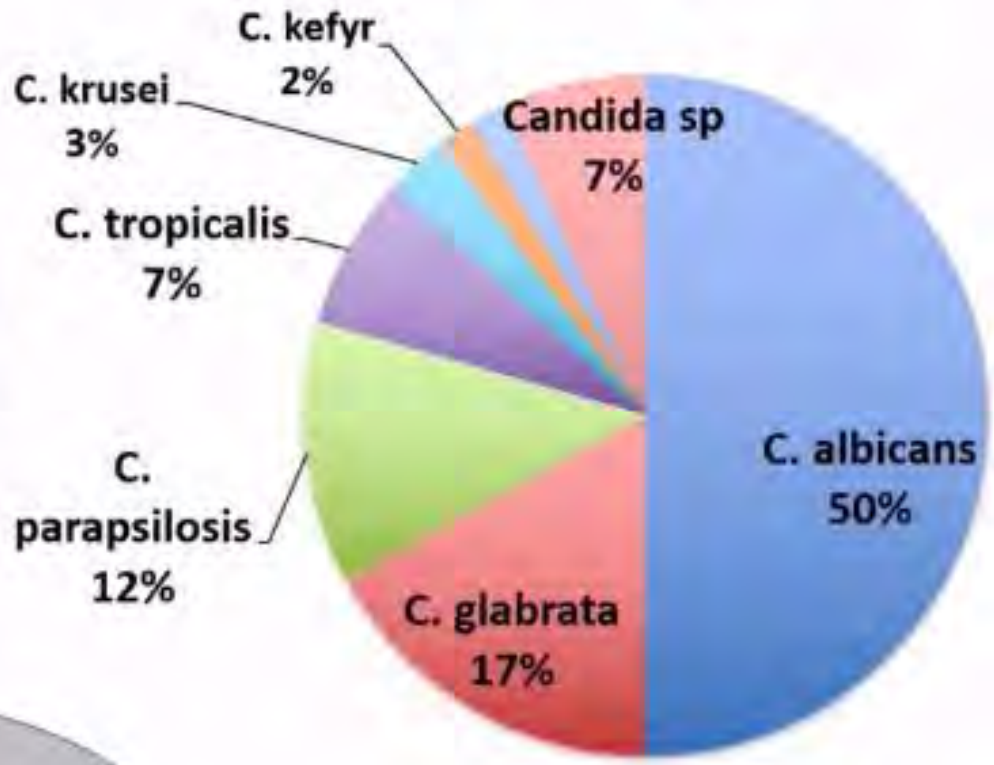
Diapositive : ME Bougnoux RICAI 2020

Candidoses invasives



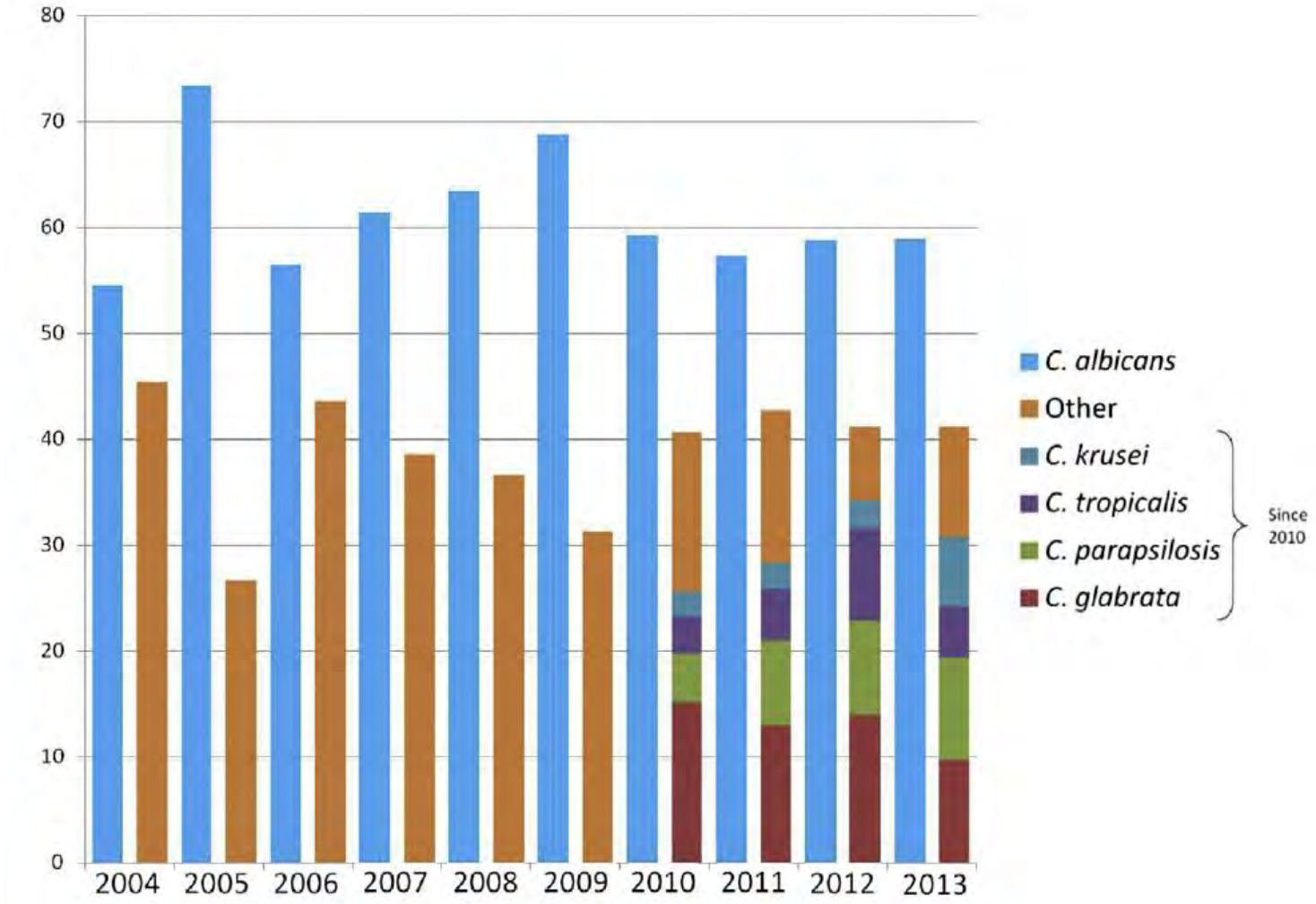
Exogène
Candida tropicalis, C. krusei
C. kefyr, C. lusitaniae

Candidémies en France :
2004-2018 : 5196 isolats
Rapport CNMRA 2018



Diapositive : ME Bougnoux RICAI 2020

Distribution of *Candida* sp in ICU patients



Baldesi *et al J Infect 2017*

Les échinocandines en 1ère position

1. Un spectre large sur *Candida*
2. Peu de problèmes de résistance à ce jour
3. Effet fongicide
4. Activité sur le biofilm
5. Peu d' effets secondaires
6. Peu d'interactions médicamenteuses (anti-rejets quand même)
7. Une supériorité/fluconazole dans une étude (Reboli et al. NEJM 2007) et sur une méta-analyse et dans des sous groupes de patients

Clinical Microbiology and Infection 22 (2016) 733.e1–733.e8

Empirical and targeted therapy of candidemia with fluconazole versus echinocandins: a propensity score–derived analysis of a population-based, multicentre prospective cohort

L.E. López-Cortés [1], B. Almirante [2], M. Cuenca-Estrella [3], J. Garnacho-Montero [4], B. Padilla [5], M. Puig-Asensio [2], I. Ruiz-Camps [2], J. Rodríguez-Baño [1, 6, *] for the members of the CANDIPOP Project from GEIH-GEMICOMED (SEIMC) and REIPI *

29 hôpitaux en Espagne, traitement empirique: 316, documenté: 421

Empirical or targeted treatment with fluconazole was not associated with increased 30-day mortality compared to echinocandins among adults with candidemia.

Initial Antifungal Strategy Reduces Mortality in Critically Ill Patients With Candidemia: A Propensity Score–Adjusted Analysis of a Multicenter Study*

José Garnacho-Montero, MD, PhD[1]; Ana Díaz-Martín, MD, PhD[2]; Luisa Cantón-Bulnes, MD[1];

TABLE 3. Multivariate Propensity Score–Adjusted Logistic Regression Model for 30- and 90-Day Mortality

Variables	30-d Mortality		90-d Mortality	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age (yr)	–		1.03 (1.01–1.06)	0.005
Underlying diseases				
Cirrhosis	3.11 (1.17–8.28)	0.023	–	
Solid cancer	–		0.41 (0.19–0.92)	0.031
Previous surgery (30 d before candidemia)	0.49 (0.25–0.97)	0.041	0.45 (0.24–0.85)	0.014
Sequential Organ Failure Assessment score at ICU admission	1.11 (1.01–1.22)	0.030	–	
C. glabrata or C. krusei	–		2.55 (1.19–5.45)	0.016
Candidemia presented with septic shock	4.32 (2.11–8.82)	< 0.001	2.81 (1.51–5.25)	0.001
Initial treatment with an echinocandin	0.32 (0.16–0.66)	0.002	0.50 (0.27–0.93)	0.029
Adequate source control (< 48 hr)	0.29 (0.15–0.58)	< 0.001	0.35 (0.19–0.65)	0.001
Breakthrough candidemia	4.38 (1.29–14.9)	0.018	–	

(*Crit Care Med* 2018; 46:384–393)

J Antimicrob Chemother 2016; **71**: 3536–3539

Comparative effectiveness of echinocandins versus fluconazole therapy for the treatment of adult candidaemia due to *Candida parapsilosis*: a retrospective observational cohort study of the Mycoses Study Group (MSG-12)

- 307 épisodes de candiémie à *C. parapsilois*
- 126: fluconazole et 181 : échinocandine
- Score de propensité (âge, sexe, race, année admission, réanimation, vasopresseurs)

Mortalité à J30: échino vs fluco : OR: 0,82, IC95% 0,33-2,07

Kathleen Chiotos

Utiliser les bonnes posologies

Molécule	Dose de charge	Dose d'entretien
Fluconazole	12mg/kg	8-10 mg/kg/j
AmB liposomiale	Non	3 mg/kg/j
Caspofungine	70 mg*	50mg/j (> 80 kg: 70mg, IHC: 35 mg**)
Micafungine	Non	100 mg/j**
Anidulafungin	200 mg	100 mg/j

* 140 mg chez les patients les plus graves (qSOFA $\geq$ 2), ** 150 mg chez les patients les plus graves, ** CI si grave

Suboptimal Dosing of Fluconazole in Critically Ill Patients: Time To Rethink Dosing

October 2020 Volume 64

Target : $AUC_{0–24}$ of 400 mg · h/liter

Eline W. Muilwijk,[a,b*] Dylan W. de Lange,[c] Jeroen A. Schouten,[d*] Roeland E. Wasmann,[a,b] Rob ter Heine,[a] David M. Burger,[a] Angela Colbers,[a] Pieter J. Haas,[e] Paul E. Verweij,[b,f] Peter Pickkers,[b,g] Roger J. Brüggemann[a,b]

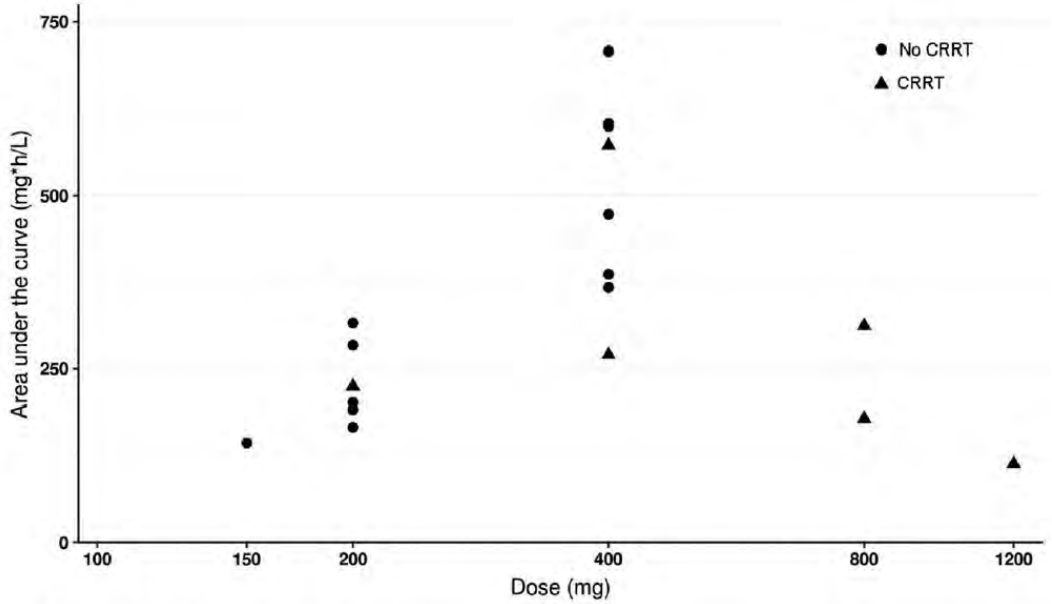


FIG 1 Daily dose of fluconazole in steady state plotted against fluconazole exposure in patients without dialysis and patients undergoing CRRT.

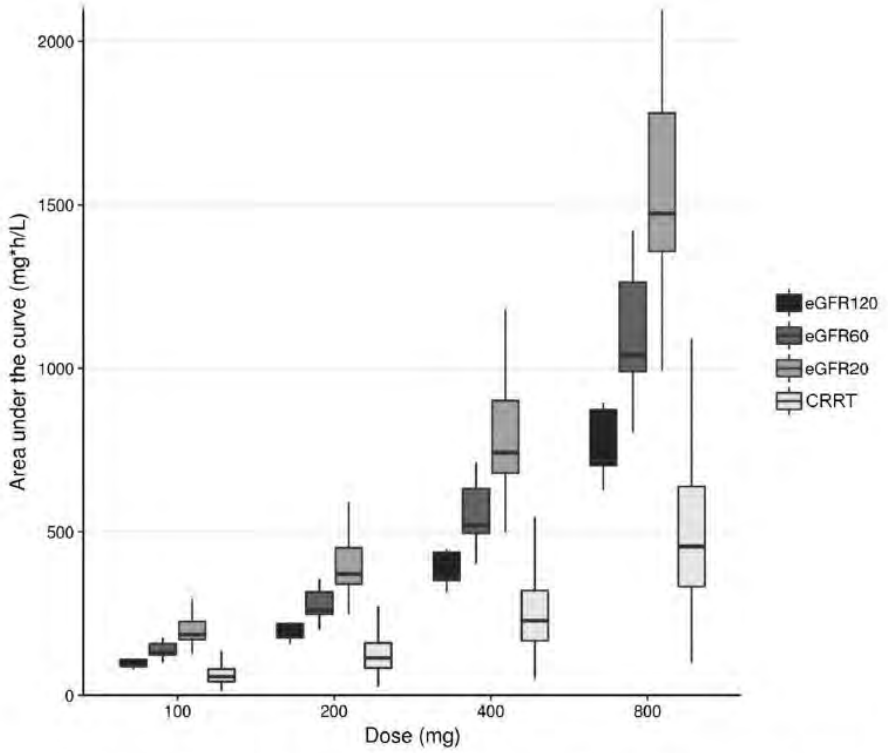


FIG 2 Simulation of fluconazole dose (100 mg – 200 mg – 400 mg – 800 mg QD) in patients with varying degrees in renal function plotted against fluconazole exposure.

- Rein normal: 600 mg/j
- Fonction rénale altérée: 400 mgj/
- EER continue: 800 mg/j

Optimization of Fluconazole Dosing for the Prevention and Treatment of Invasive Candidiasis Based on the Pharmacokinetics of Fluconazole in Critically Ill Patients

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

2021

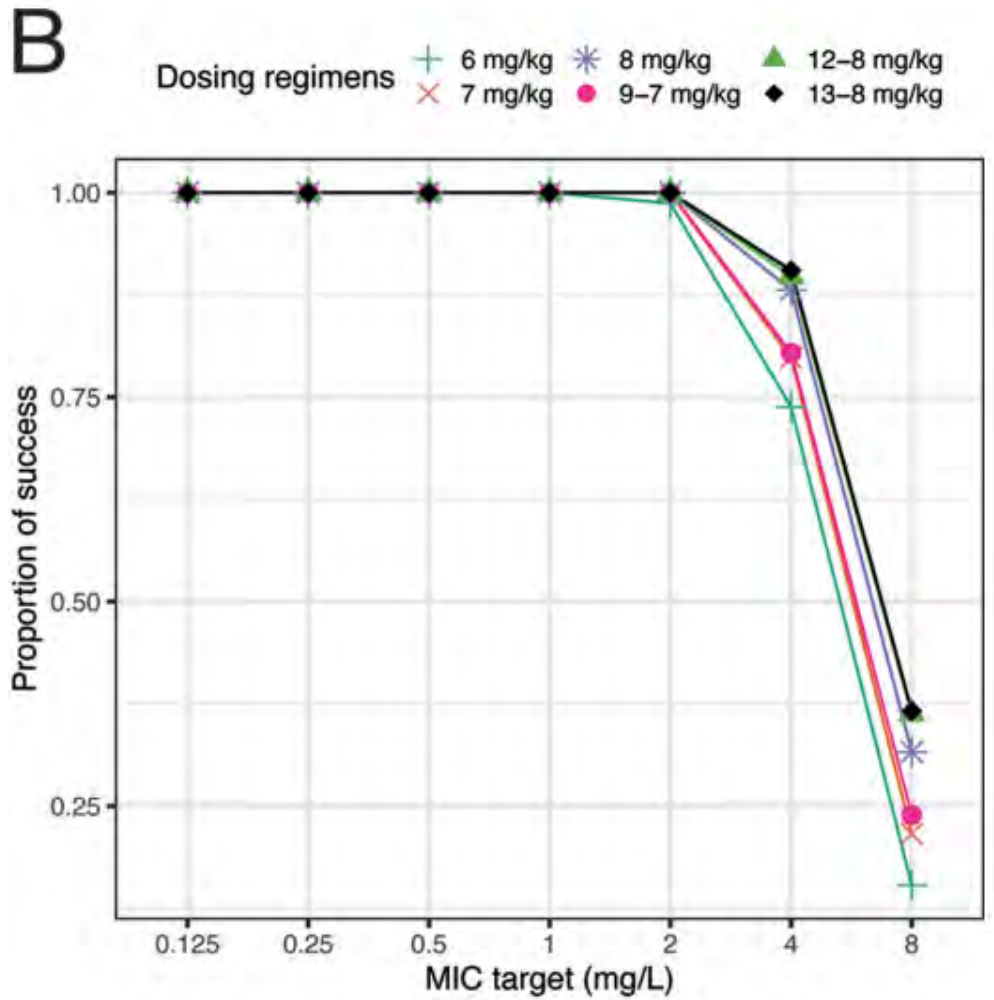
JM Boonstra et coll.

fAUC/MIC of 100 and MIC of ≥ 2 mg/liter

Fixed dosing regimen	PTA for fixed dosing (%)		
	Day 1	Day 3	Day 5
400 mg daily	16	87	97
600 mg daily	60	98	100
800 mg loading + 400 mg daily	87	96	97
1,000 mg loading + 600 mg daily	94	100	100
1,000 mg loading + 800 mg daily	94	100	100
1,200 mg loading + 1,000 mg daily	98	100	100

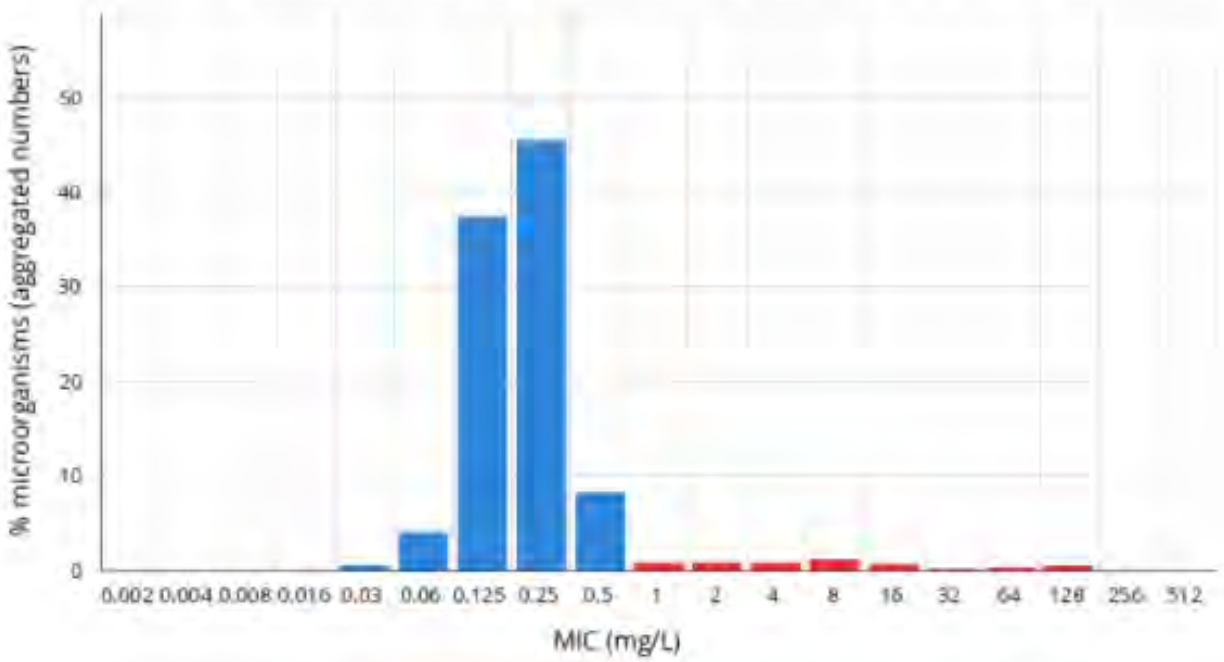
[a]Abbreviation: PTA, probability of target attainment.

Wt-based dosing regimen	PTA for wt-based dosing (%)		
	Day 1	Day 3	Day 5
6 mg/kg daily	36	97	99
7 mg/kg daily	58	98	100
8 mg/kg daily	73	100	100
9 mg/kg loading + 7 mg/kg daily	83	99	100
12 mg/kg loading + 8 mg/kg daily	94	100	100
13 mg/kg loading + 8 mg/kg daily	96	100	100



Fluconazole / Candida albicans EUCAST
International MIC distribution - Reference database 2022-03-13
Based on aggregated distributions

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

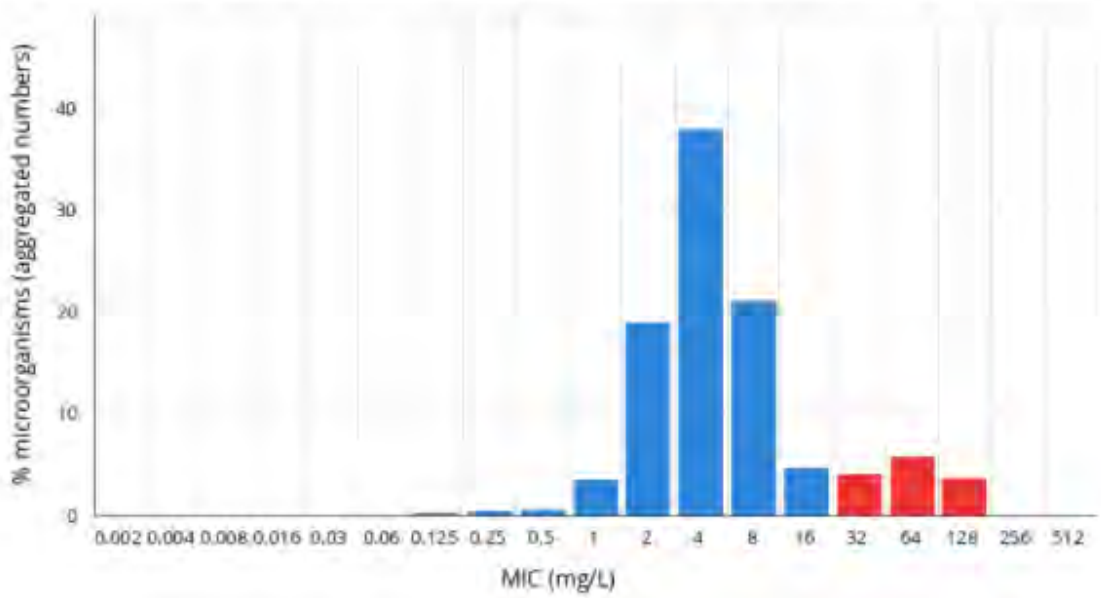


MIC
Epidemiological cut-off (ECOFF): 0.5 mg/L
Wildtype (WT) organisms: ≤ 0.5 mg/L

Confidence Interval: -
2175 observations (5 data sources)

Fluconazole / Candida glabrata EUCAST
International MIC distribution - Reference database 2022-03-13
Based on aggregated distributions

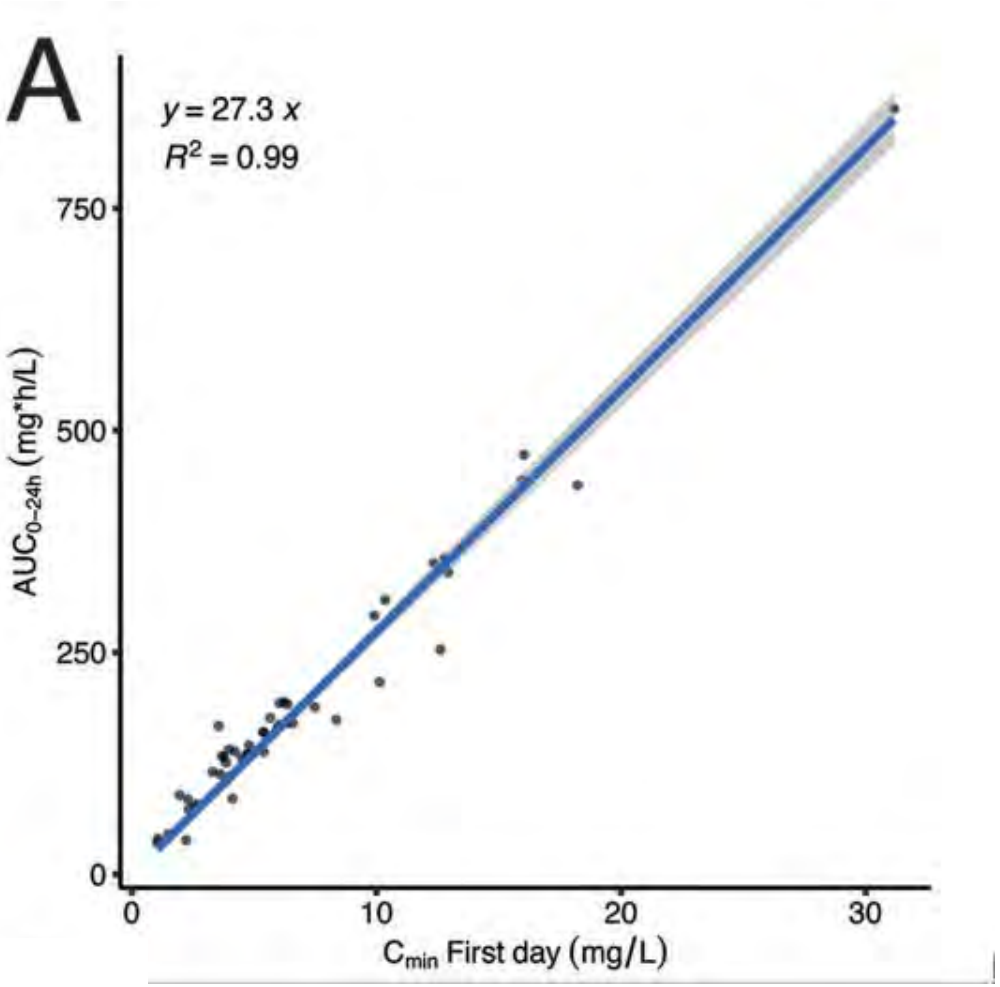
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

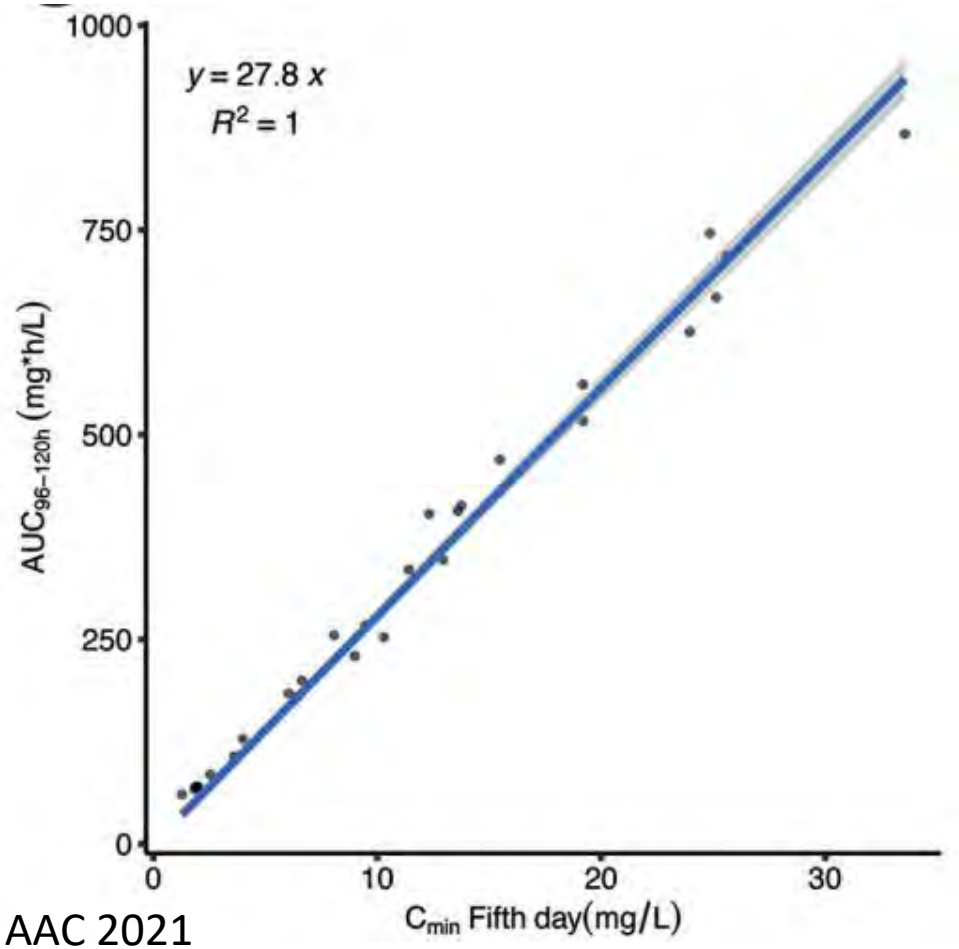


MIC
Epidemiological cut-off (ECOFF): 16 mg/L
Wildtype (WT) organisms: ≤ 16 mg/L

Confidence Interval: -
1289 observations (8 data sources)

Bonne relation entre concentrations résiduelles de fluconazole et ASC





JM Boonstra et coll. AAC 2021

Impact of Loading Dose of Caspofungin in Pharmacokinetic-Pharmacodynamic Target Attainment for Severe Candidiasis Infections in Patients in Intensive Care Units: the CASPOLOAD Study

Sébastien Bailly,[a] Elodie Gautier-Veyret,[a,b] Minh P. Lê,[c,d] Lila Bouadma,[e,f] Olivier Andremont,[e] Mathilde Neuville,[e,f] Bruno Mourvillier,[g,h] Romain Sonneville,[e,f,g,h,i] Eric Magalhaes,[e] Jordane Lebut,[e] Aguila Radjou,[e] Roland Smonig,[e] Michel Wolff,[e,f] Laurent Massias,[c,d,e,f] Claire Dupuis,[j] Jean-François Timsit[e,f]

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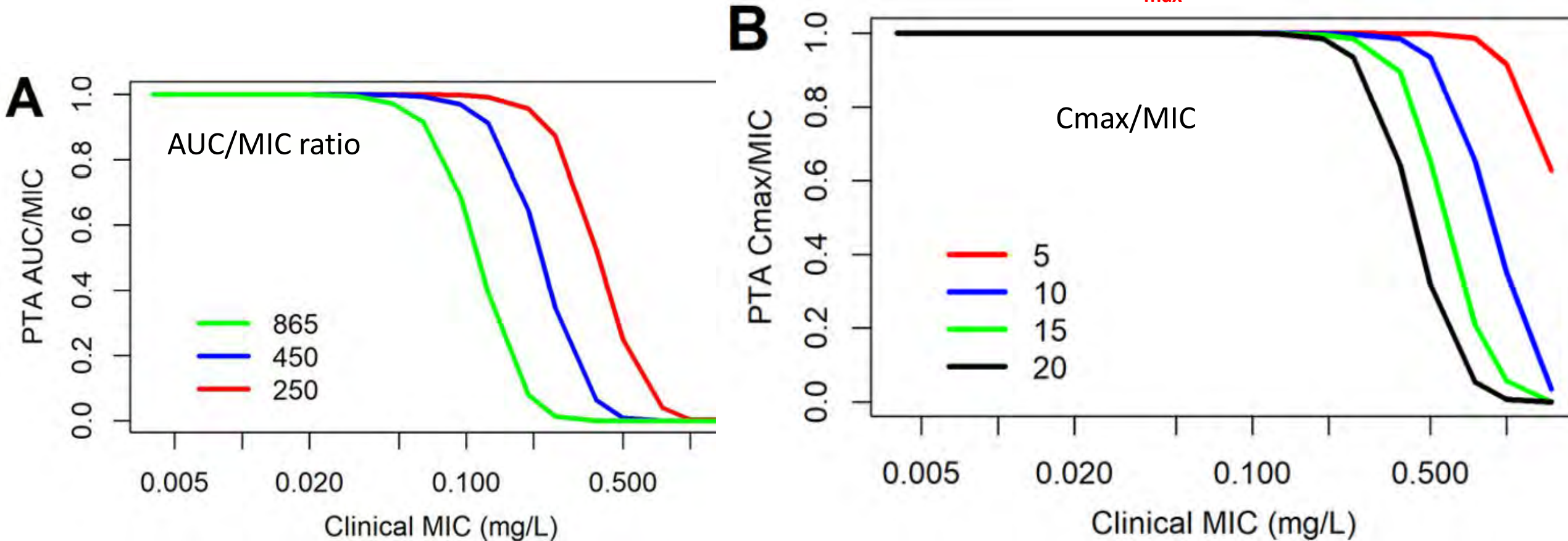
December 2020

We showed that the loading dose of 140 mg in ICU patients enabled the achievement of a PTA of 90% for MICs below or equal to 0.19 and 0.5 mg/liter for PK-PD targets of AUC/MIC = 250 and C_{max}/MIC = 10, respectively



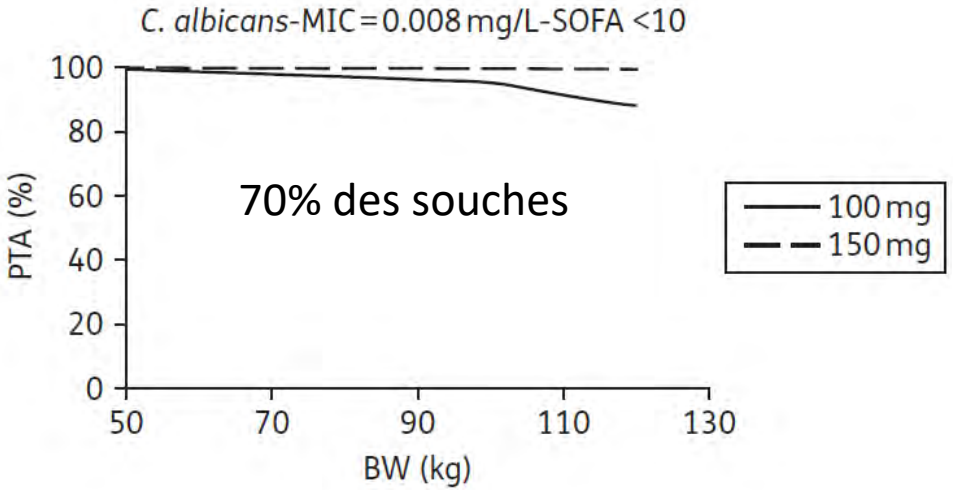
Population pharmacokinetics of micafungin in ICU patients with sepsis and mechanical ventilation

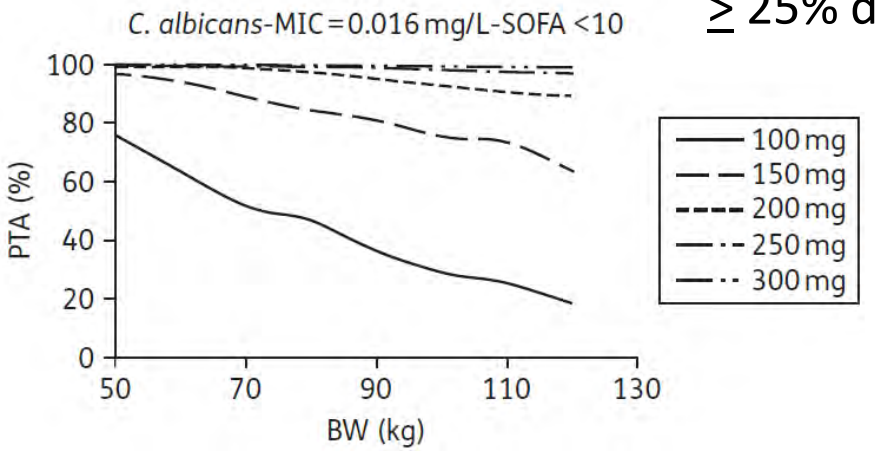
J Antimicrob Chemother
doi:10.1093/jac/dkw352

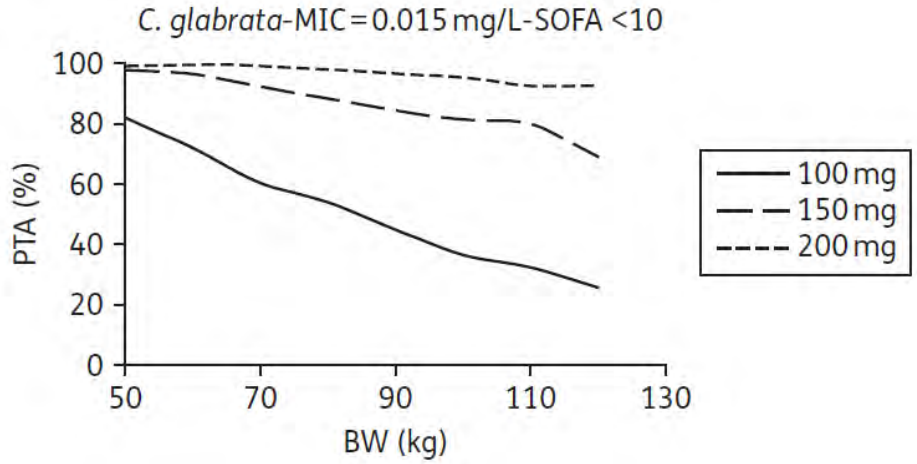
Vincent Jullien[1]*, Elie Azoulay[2], Carole Schwebel[3], Thomas Le Saux[1], Pierre Emmanuel Charles[4], Muriel Cornet[5], Bertrand Souweine[6], Kadda Klouche[7], Samir Jaber[8], Jean-Louis Trouillet[9], Fabrice Bruneel[10], Martin Cour[11], Joel Cousson[12], Ferhat Meziani[13], Didier Gruson[14], Adeline Paris[15], Michael Darmon[16], Maité Garrouste-Orgeas[17], Jean-Christophe Navellou[18], Arnaud Foucrier[19], Bernard Allaouchiche[20], Vincent Das[21], Jean-Pierre Gangneux[22], Stéphane Ruckly[23], Michel Wolff[24,25] and Jean-François Timsit[24,25] on behalf of the EMPIRICUS Trial Study Group†

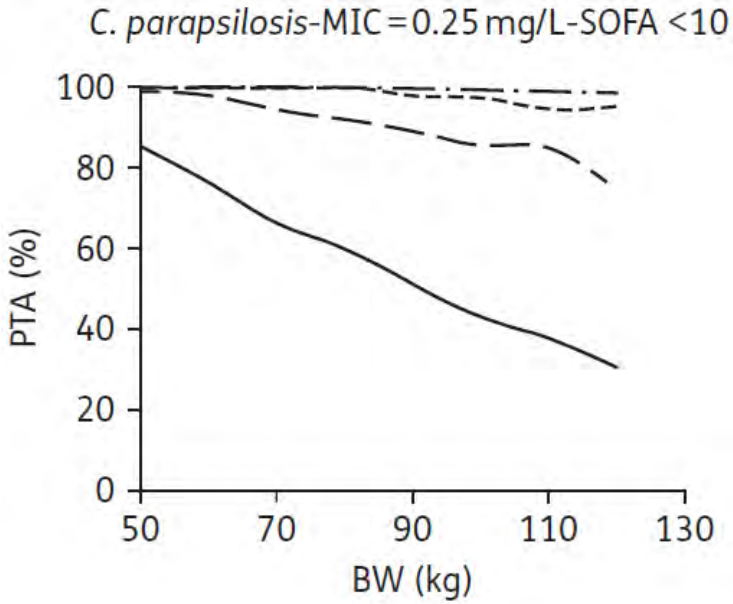
8/9/2016

≥ 25% des souches



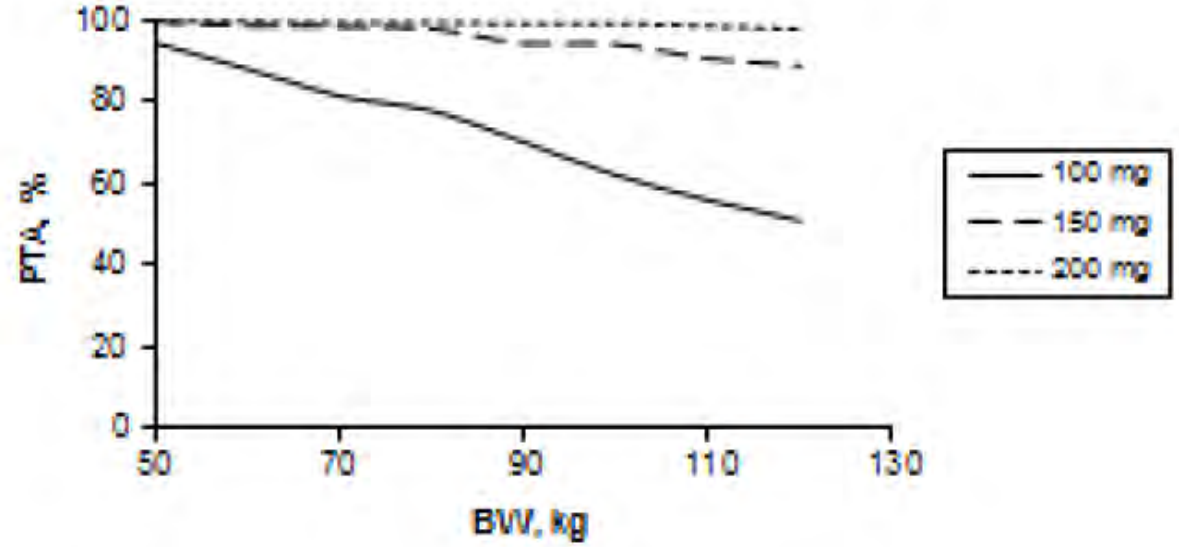






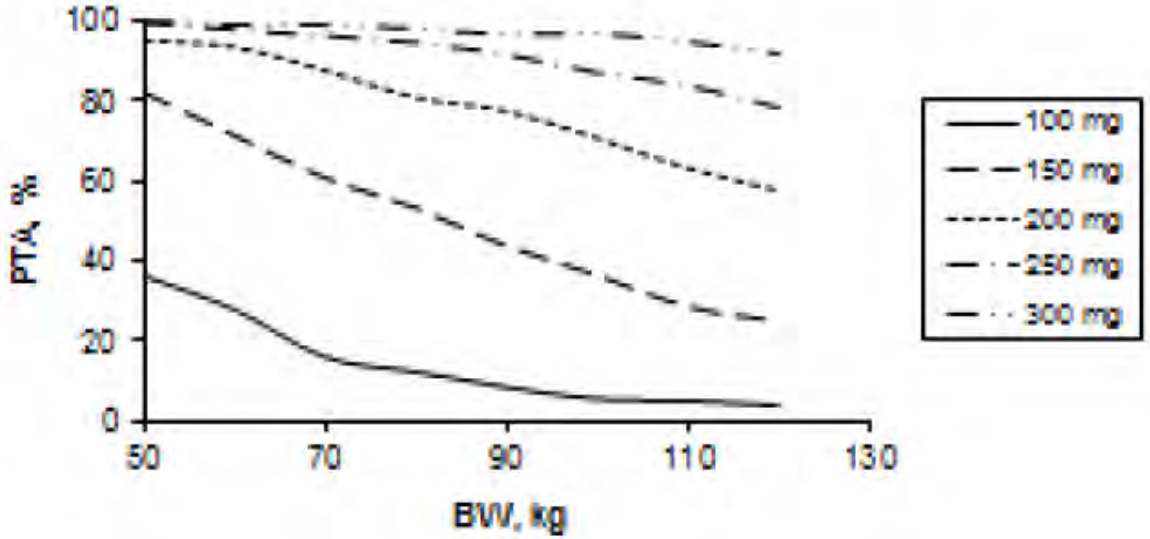
C. Albicans – MIC = 0.016 mg/L - SOFA ≥ 10

B



C. Glabrata - MIC = 0.03 mg/L - SOFA ≥ 10

B

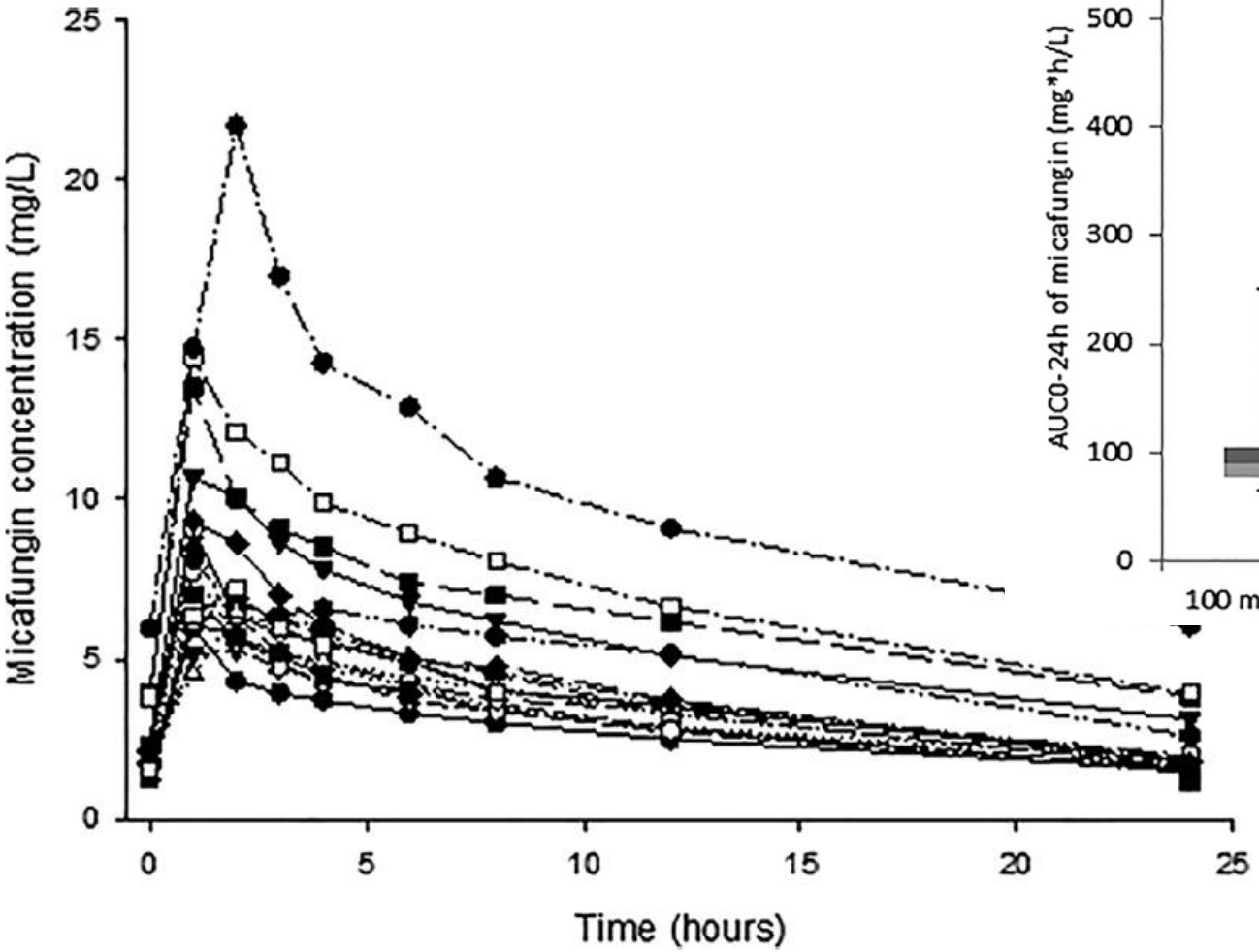


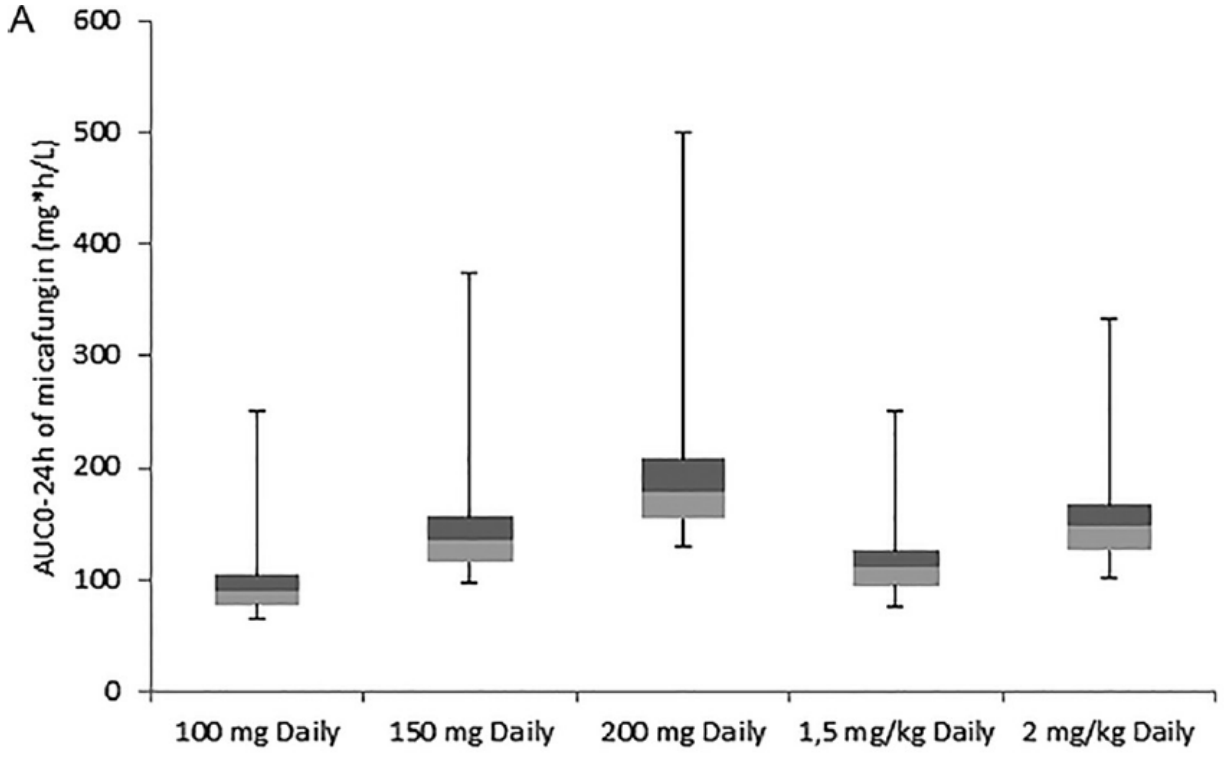
Pharmacokinetic Properties of Micafungin in Critically Ill Patients Diagnosed with Invasive Candidiasis

J. M. Boonstra,[a] K. C. van der Elst,[a] A. Veringa,[a] E. M. Jongedijk,[a] R. J. Brüggemann,[b] R. A. Koster,[a] G. A. Kampinga,[c] J. G. Kosterink,[a,d] T. S. van der Werf,[e,f] J. G. Zijlstra,[g] D. J. Touw,[a] J. W. C. Alffenaar[a]

Antimicrobial Agents and Chemotherapy®

December 2017 Volume 61



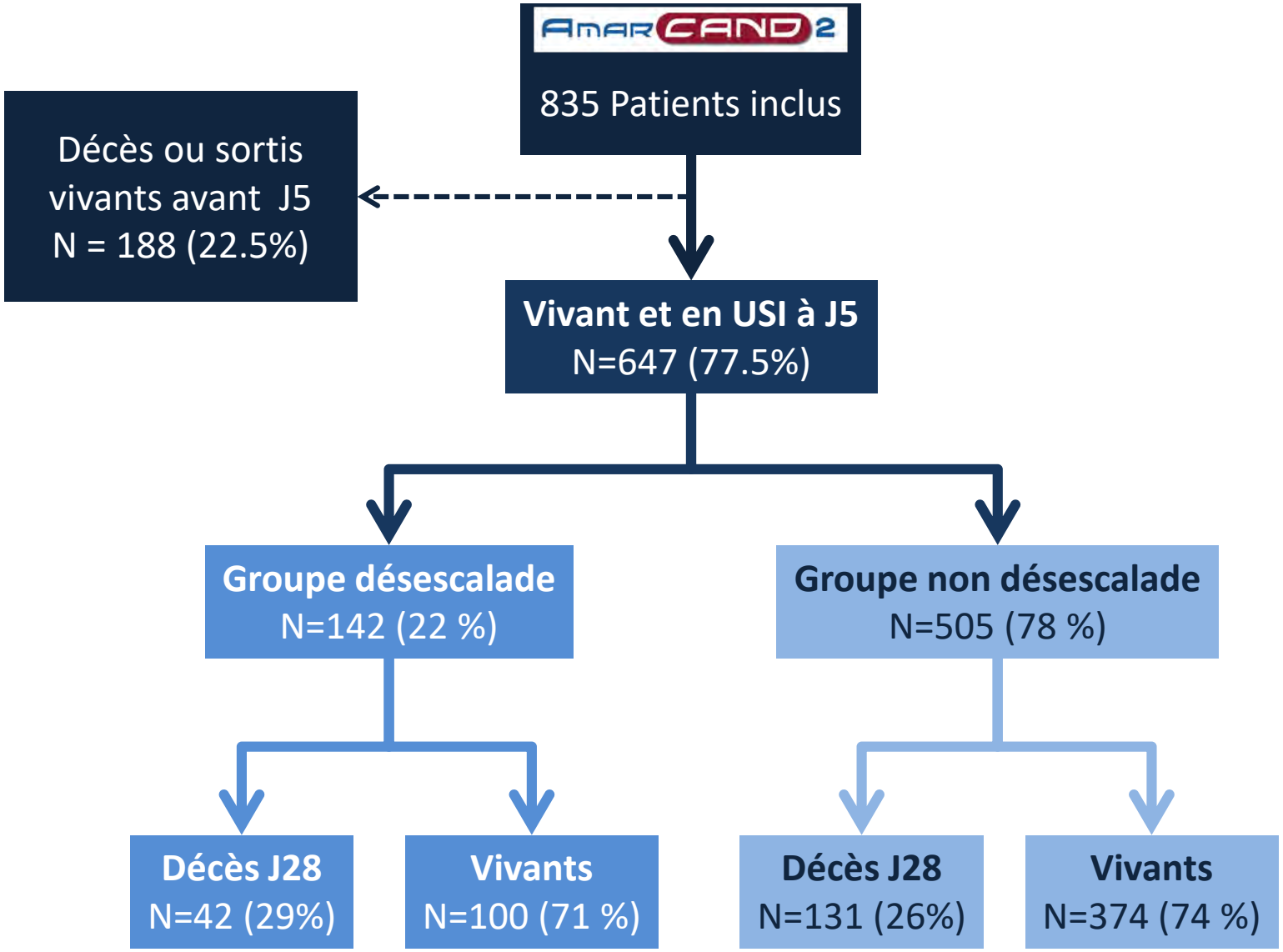


Arrêt précoce et désescalade?

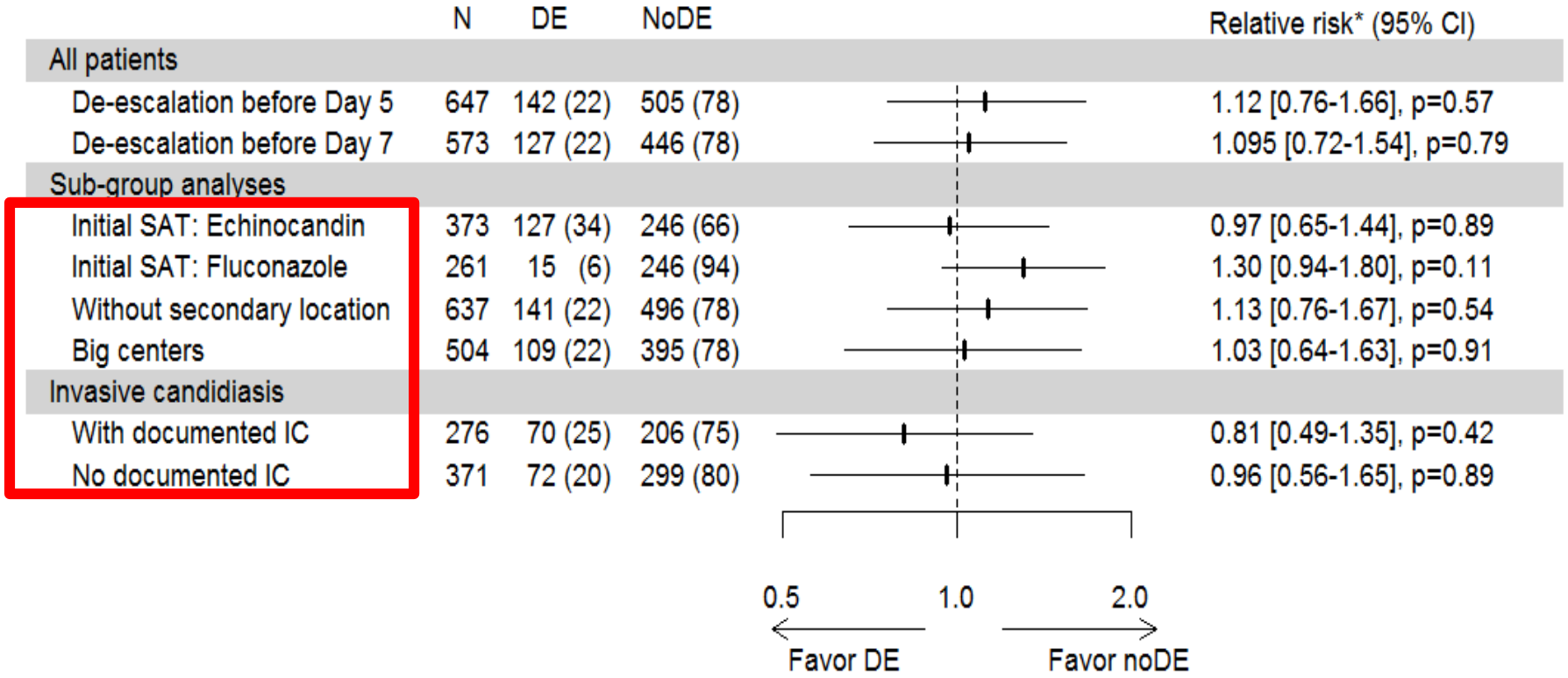
- La pression de sélection reste avant tout liée aux traitements empiriques/préemptifs qui représentent 80% des traitements
- Traitement empirique/préemptif a rediscuter à J5

4. Transition from an echinocandin to fluconazole (usually within 5–7 days) is recommended for patients who are clinically stable, have isolates that are susceptible to fluconazole (eg, *C. albicans*), and have negative repeat blood cultures following initiation of antifungal therapy *(strong recommendation; moderate-quality evidence)*.

IDSA 2016



Bailly S et al. Intensive Care Med 2015



Pas d'effet significatif de la désescalade précoce sur la mortalité à J28 pour les différents sous groupes

Pas d'effet significatif de l'arrêt précoce du traitement sur la mortalité à J28

Bailly S et al. Intensive Care Med 2015

Clinical Infectious Diseases

MAJOR ARTICLE

Rezafungin Versus Caspofungin in a Phase 2, Randomized, Double-blind Study for the Treatment of Candidemia and Invasive Candidiasis: The STRIVE Trial

George R. Thompson III,[1] Alex Soriano,[2] Athanasios Skoutelis,[3] Jose A. Vazquez,[4] Patrick M. Honore,[5] Juan P. Horcajada,[6] Herbert Spapen,[7] Matteo Bassetti,[8] Luis Ostrosky-Zeichner,[9] Anita F. Das,[10] Rolando M. Viani,[11] Taylor Sandison,[11] and Peter G. Pappas[12]; The STRIVE Trial Investigators

Clinical Infectious Diseases® 2021;73(11):e3647–55

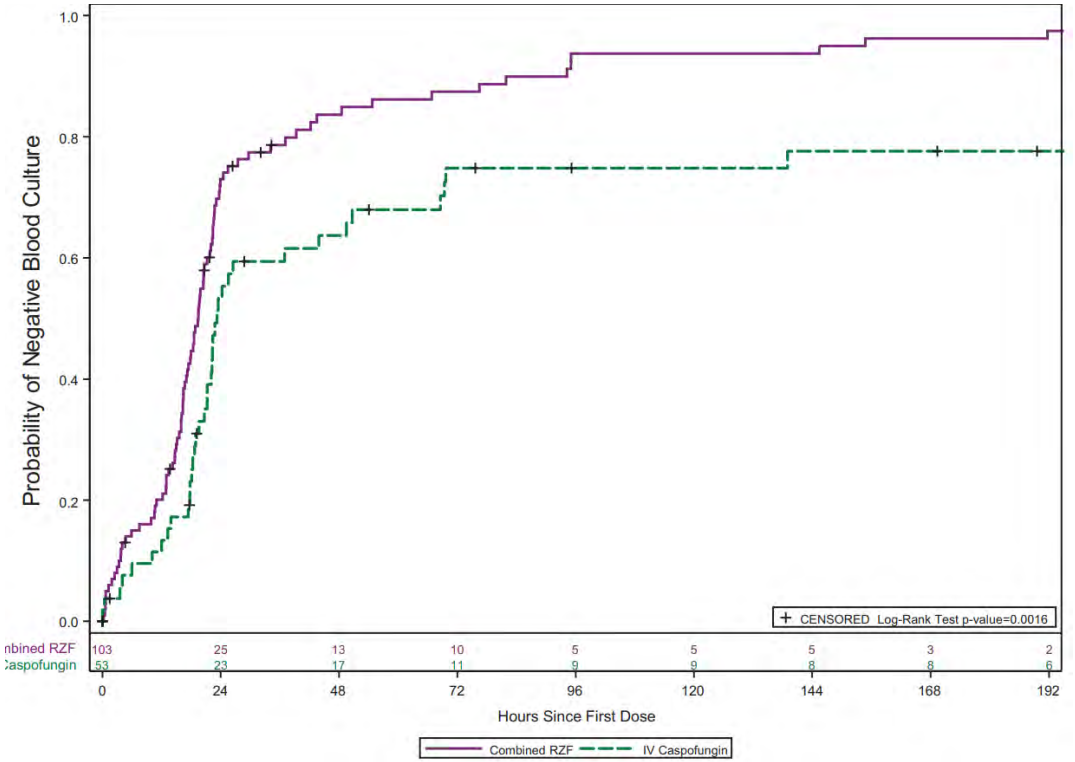
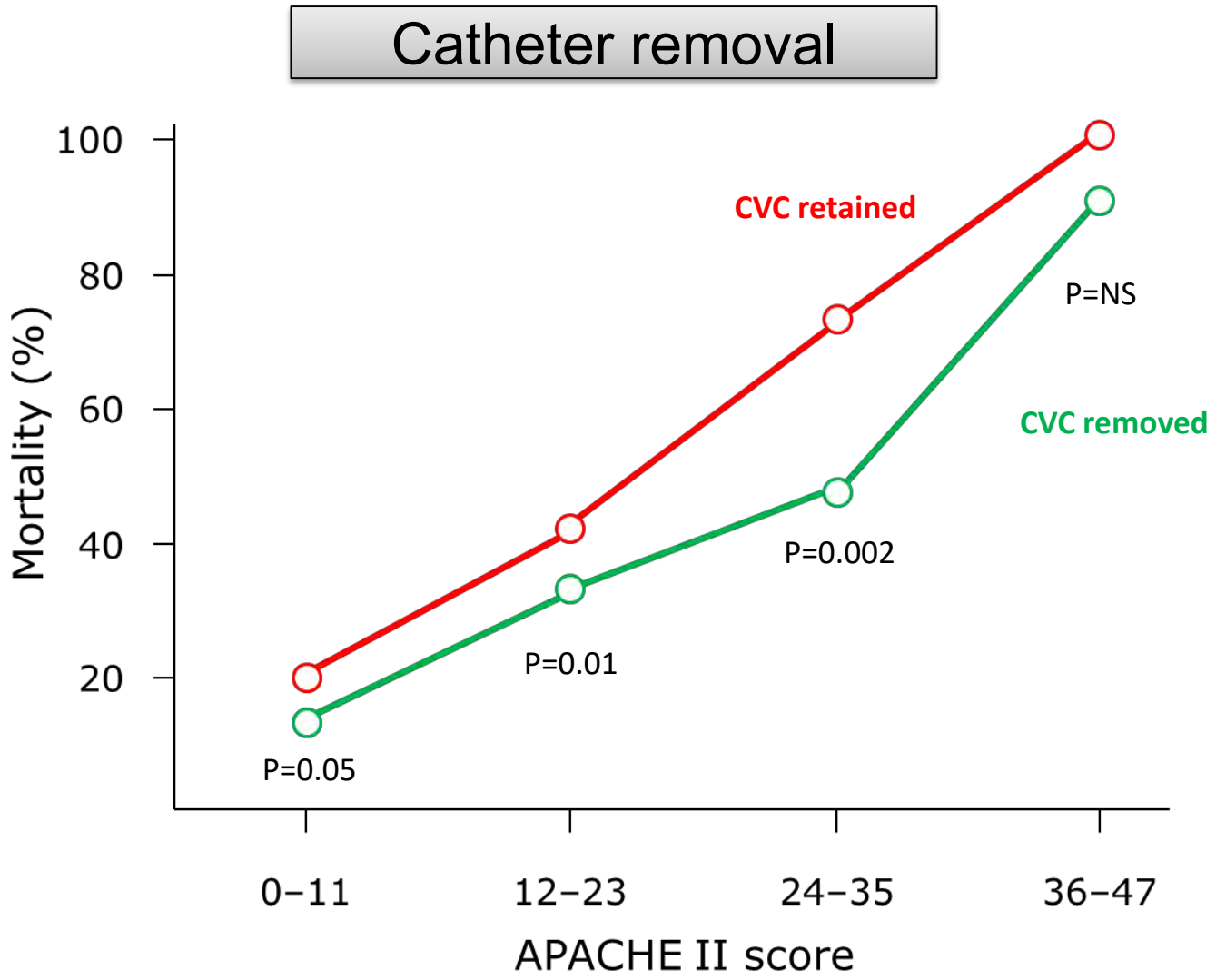


Table 3. Primary Efficacy Endpoint: Overall Response at Day 14 (Microbiological Intent-to-Treat [mITT] Population)—Part A, Part B, and Combined

Overall Response, n (%)	Rezafungin Once Weekly 400 mg	Rezafungin Once Weekly 400 mg/200 mg	Caspofungin Once Daily 70 mg/50 mg
		Combined (Part A + Part B)	
	N = 76	N = 46	N = 61
Overall cure [95% CI[a]]	46 (60.5) [48.6–71.6]	35 (76.1) [61.2–87.4]	41 (67.2) [54.0–78.7]
Failure/indeterminate	30 (39.5)	11 (23.9)	20 (32.8)
Failure	20 (26.3)	8 (17.4)	17 (27.9)
Indeterminate	10 (13.2)	3 (6.5)	3 (4.9)

Impact of treatment strategy on outcomes



Andes DR, et al. Clin Infect Dis 2012;54:1110–22

Candidémies: durée du traitement antifongique

	Sans complications	Complications
Non neutropéniques	14 j après dernière H + Switch oral précoce	4-8 semaines

Discuter

- ETT/ ETO (⇨ 8% d'endocardites) : signes cliniques d'EI, H+ soutenues
- FO (⇨ 16% de choriorétinites): malade non conscient ou symptomatique ?

Candidémies d'origine urinaire

- Fluconazole ou fluconazole forte dose 12 mg/kg/j) si *C. glabrata* avec CMI < 32 mg/L

- Ampho B déoxycholate pour *C. krusei* et *C. glabrata* résistant au fluconazole

Traitement des endocardites à *Candida*

	Molécules	Durée
Phase initiale	AmB liposomale (3-5 mg/kg/j) +/- flucytosine: 25 mg/kg x 4/J ou Caspofungine (150 mg/j) ou Micafungine (150 mg/j)	4 à 6 semaines
Relais oral	Fluconazole	A discuter à J1 et en tt suspensif (si pas de chirurgie)*

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

* Modifié

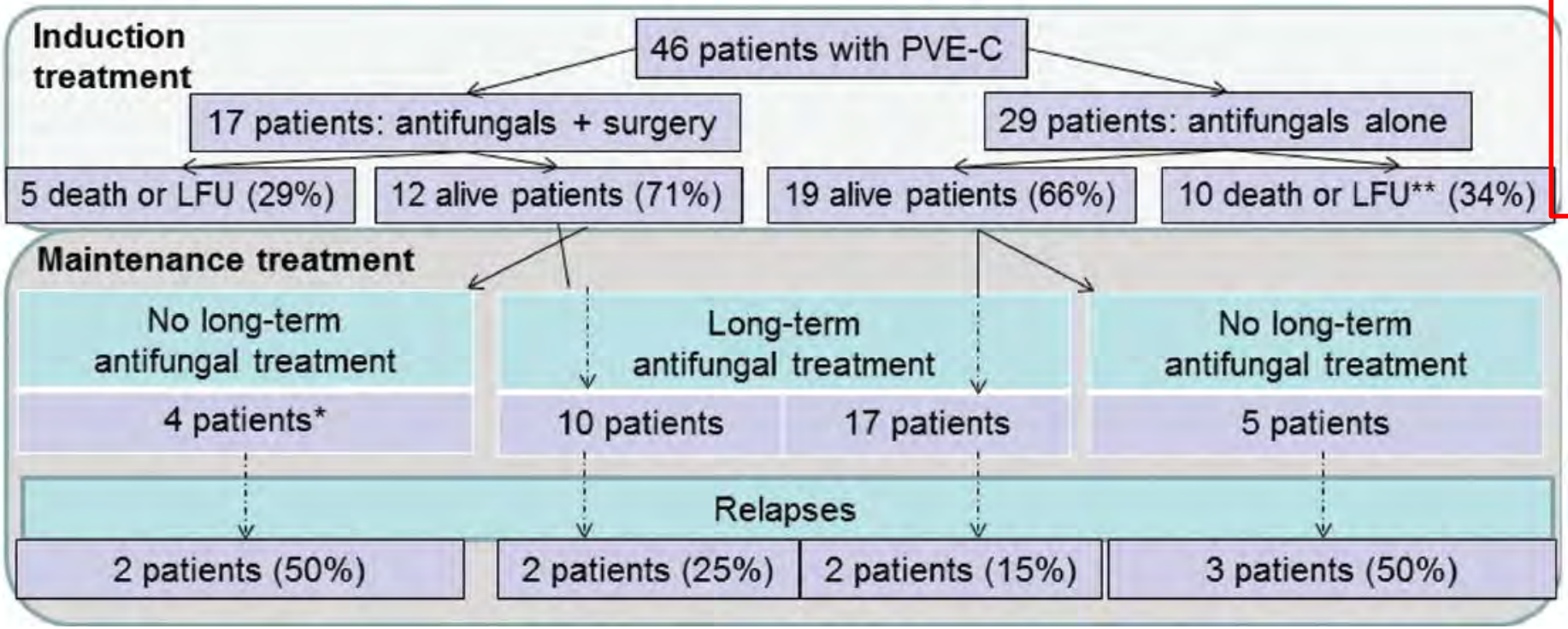
Clinical Infectious Diseases
MAJOR ARTICLE

Prosthetic Valve *Candida* spp. Endocarditis: New Insights Into Long-term Prognosis—The ESCAPE Study

Claire Rivoisy,[1,a] Antonio Vena,[2,3,4,5,a] Laura Schaeffer,[6] Caroline Charlier,[1] Arnaud Fontanet,[6,7] François Delahaye,[8] Emilio Bouza,[4,5,9] Olivier Lortholary,[1,10,b] Patricia Munoz,[2,3,4,5,b] and Agnès Lefort[11,12,b]; for the French Mycoses Study Group and Grupo de Apoyo al Manejo de las Endocarditis en España (GAMES)[c]

Clinical Infectious Diseases®
2018;66(6):825–32

Patients who received L-amB alone had a better 6-month survival rate than those who received an echinocandin alone (aOR, 13.52; 95% CI, 1.03–838.10).



"Maintenance" fluconazole therapy, prescribed in 27 patients for a median duration of 13 months (range, 2–84 months), led to minor adverse effects.

UNIKLINIK KÖLN

EQUAL *Candida* Score – Guideline Adherence

EQUAL Candida Score 2018: An **ECMM** Score Derived From Current Guidelines to Measure **QUAL**ity of Clinical Candidemia Management

Mellinghoff SC[1,2], Rutz J[1], Cornely OA[1,2]
[1] Department I for Internal Medicine, Excellence Center for Medical Mycology (ECMM), University of Cologne, Germany,
[2] CECAD Cluster of Excellence, University of Cologne, Germany
DOI: 10.4126/FRL01-006411743

Background

The EQUAL Candida Score weighs and aggregates factors recommended for the ideal management of candidemia and provides a tool for antifungal stewardship as well as for measuring guideline adherence. Current guidelines provided by the European Society for Clinical Microbiology and Infectious Diseases[4,5] and by the Infectious Diseases Society of America[3] were reviewed and the strongest recommendations for management quality selected as basis for this scoring tool.

Maximum Score

Non-CVC carriers		CVC carriers	
Diagnosis	10	Diagnosis	10
Treatment	7	Treatment	10
Follow-up	2	Follow-up	2
Total	19	Total	22

References

1. Mellinghoff et al. *Mycoses* 2018; 2. Koehler et al. *Mycoses* 2014; 3. Pappas et al. *Clin Infect Dis* 2016; 4. Cuenca-Estrella et al. *Clin Infect Dis* 2012; 5. Cornely et al. *Clin Microbiol Infect* 2012; 6. Munoz et al. *Diagn Microbiol Infect Dis* 2017; 7. Andes et al. *Clin Infect Dis* 2012.

EQUAL Candida Score 2018 [1,2]

Diagnosis	Initial blood culture (40mL) [3,4]	3
	Species identification [3,4]	3
	Susceptibility testing [3,4]	2
	Echocardiography [3,5]	1
	Ophthalmoscopy [5,6]	1
Treatment	Echinocandin treatment [3,5]	3
	Step down to fluconazole depending on susceptibility result [3,5]	2
	Treatment for 14 days after first negative follow-up culture [3,5]	2
	CVC carriers*: CVC removal [3,5,7] ≤ 24 hours from diagnosis	3
	CVC carriers*: CVC removal [3,5,7] > 24 < 72 hours from diagnosis	2
Follow-Up	Follow-up blood culture (at least one per day until negative) [3,5]	2

* CVC carriers receive extra points, total score thus differs in Non-CVC vs. CVC carriers

UNIKLINIK KÖLN

December 2018

ECMM

DOI: 10.1111/myc.13376

ORIGINAL ARTICLE

mycoses WILEY

Mycoses. 2021;64:1512–1520.

Increasing morbidity and mortality of candidemia over one decade in a Swiss university hospital

Julien Battistolo[1] | Emmanouil Glampedakis[1,2] | Lauro Damonti[1,3] | Julien Poissy[1,4] | Bruno Grandbastien[2] | Laetitia Kalbermatter[2] | Jean-Luc Pagani[5] | Philippe Eggimann[6] | Pierre-Yves Bochud[1] | Thierry Calandra[1] | Oscar Marchetti[1,7] | Frederic Lamoth[1,8] | the Fungal Infection Network of Switzerland (FUNGINOS)

	Period 1 (2004-2006) n = 68	Period 2 (2014-2017) n = 102	*p*-value
First line antifungal treatment[a]			
Fluconazole	51 (75)	25 (24)	**<.01**
Echinocandin	7 (10)	57 (56)	**<.01**
Other / unspecified	4 (6)	9 (9)	.56
None	6 (9)	11 (11)	.80
Characteristics of treatment/interventions			
Delay from blood culture sampling to start antifungal therapy, days	2 (1-3)	2 (2-3)	.89
Duration of antifungal therapy, days	19 (14-36)	16 (14-24)	**.02**
Change of CVC[b]	57 (93)	56 (67)	**<.01**
Surgical drainage	9 (13)	21 (21)	.30
Infectious diseases consultation	59 (87)	74 (73)	.11
Outcome			
ICU admission after candidemia[c]	8 (12)	42 (41)	**<.01**

Fig. 2. Countries from which *Candida auris* cases have been reported, as of February 15, 2021 https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html#historical.

C auris spread

1. Rapidly emerging nosocomial pathogen isolated from most continents with no direct or indirect travel link
2. Strong biofilm formation → persistent and invasive infections.
3. Difficult early diagnosis (MALDI-TOF with updated database and DNA sequencing)
4. Intrinsic resistance to azoles and variable resistance to amphotericin B. Few isolates showing panresistance have been reported.
5. Echinocandins are the treatment of choice for *C. auris* infection.
6. Guidelines on prevention of spread of *C. auris* are similar to MDRO + environmental disinfection with sporicidical agent.

Conclusions

Action

- Restrict antifungal prophylaxis
- Start prompt ‘early’ antifungal treatment based on risk factors
- Select an antifungal agent that the isolate is susceptible to
- Achieve adequate source control
- Use an adequate dose: low dose is associated with resistance
- Stop ‘early’ inappropriate therapy
- De-escalate whenever possible
- Check duration of therapy

Bassetti M et al. JAC 2016